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PAN-CANADIAN
ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review Initial Clinical Guidance Report

Olaparib (Lynparza) for Ovarian Cancer

October 3, 2019

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1 GUIDANCE IN BRIEF

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding olaparib (Lynparza) for ovarian cancer. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature olaparib (Lynparza) for ovarian cancer conducted by the Genitourinary Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; input from Registered Clinicians; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on olaparib (Lynparza) for ovarian cancer, a summary of submitted Provincial Advisory Group Input on olaparib (Lynparza) for ovarian cancer, and a summary of submitted Registered Clinician Input on olaparib (Lynparza) for ovarian cancer, and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The objective of this review is to evaluate the safety and efficacy of olaparib (Lynparza) as maintenance treatment for adult patients with platinum-sensitive (complete or partial response to first-line platinum-based chemotherapy) advanced stage ovarian, primary peritoneal, and/or fallopian tube cancer patients with somatic or germline BRCA mutations that were deleterious or suspected to be deleterious.

The appropriate comparator for olaparib in this treatment setting is best-supportive care. Bevacizumab maintenance therapy is also available but is used infrequently in the Canadian setting. Olaparib has a Health Canada market authorization for maintenance treatment of adult patients with advanced BRCA-mutated high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) to first-line platinum-based chemotherapy. Patients must have confirmation of BRCA mutation (identified by either germline or tumour testing) before olaparib treatment is initiated. An NOC was issued by Health Canada for olaparib for this indication on May 03, 2019.

Olaparib (Lynparza) is a first-in-class, oral, potent inhibitor (ADP-ribose) polymerase (PARP). Olaparib represents the first targeted medicine in ovarian cancer. The recommended total daily dose of olaparib tablets is 600 mg, taken orally as two 150 mg tablets twice daily. Patients can continue treatment for 2 years or until disease progression. Patients with a complete response (no radiological evidence of disease) at 2 years should stop treatment. Patients with evidence of disease at 2 years, who in the opinion of the treating physician can derive further benefit from continuous treatment, can be treated beyond 2 years.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included one randomized controlled trial (RCT), the SOLO1 trial (N=391), and the results are summarized below.

SOLO1

SOLO1 was an international, multi-centre, double-blinded, placebo-controlled, phase III, superiority RCT of olaparib versus placebo in the maintenance setting of platinum-sensitive (complete or partial response to first-line platinum-based chemotherapy) advanced (FIGO Stage III-IV) stage ovarian, primary peritoneal, and/or fallopian tube cancer patients with somatic or germline BRCA mutations that were deleterious or suspected to be deleterious. Eligible patients were randomised in a 2:1 ratio to receive either 300mg of olaparib twice daily or matching placebo twice daily. A total of 260 patients were randomized and treated in the olaparib arm and 131 patients were randomized (and 130 treated) in the placebo arm. Participants continued treatment until investigator-assessed progressive disease (PD) as per RECIST 1.1 (unless in the investigator's opinion there was clinical benefit to continue treatment), patient decision, unacceptable toxicity due to adverse events (AEs), bone marrow findings consistent with myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML), or if at completion of 2 years of treatment there was no evidence of disease.¹

The primary endpoint of SOLO1 was progression-free survival (PFS), and secondary outcomes included second progression-free survival (PFS2; defined as time to second progression or death event following a primary progression event) and overall survival (OS) that were controlled for multiplicity. Additional exploratory secondary outcomes included time to first subsequent therapy or death (TFST); time to second subsequent therapy or death (TSST); time to study discontinuation or death (TDT); time to earliest progression by RECIST 1.1, CA-125, or death; best overall response (BoR), and health-related quality of life (HRQoL). Objective response outcomes were assessed by the investigator (ie., PFS, PFS2, BoR) and a sensitivity analysis using blinded independent central review (BICR) was conducted. Several sensitivity analyses for the primary outcome of PFS were also conducted to evaluate for potential biases (see Section 6 for details). HRQoL was assessed using the Trial Outcome Index (TOI), derived from the Functional Assessment of Cancer Therapy - Ovarian (FACT-O) questionnaire. The TOI is an index composed of physical and functional well-being, and additional concerns scales from the FACT-O questionnaire and is considered to target the most relevant symptoms together with function and physical well-being and can be directly related to signs and symptoms of AEs. Safety was monitored regularly throughout the study and included all patients who received at least 1 dose of the assigned combination treatment.¹

The median age was 53.0 years of age in both treatment arms, and most patients were White (81.8%).^{1,2} In both treatment arms, 82% of patients experienced a CR following first-line platinum therapy and 18% experienced a PR. Overall, the majority of patients had an ECOG PS of 0 (n=305; 78%); a primary tumor location in the ovary (n=333; 85%); CA-125 level \leq ULN (n=370; 94.6%); and a serous histologic subtype (n=376; 96%). Less patients in the olaparib treatment arm reported 6 cycles of treatment (n=198; 76%) compared to the placebo arm (n=106; 81%). More patients in the olaparib arm (n=58; 22%) were treated with 7-9 cycles of platinum-based therapy compared to patients who received placebo (n=24; 18%).¹ More patients in the olaparib group had FIGO stage III (n=220, 85%) compared to the placebo group (n=105, 80%), with stage FIGO IIIC being the most common in both treatment arms (68.5% and 69.5% in the olaparib and placebo arms, respectively), and more patients in the olaparib arm with FIGO stage IIIB compared to the placebo arm

(10.4% compared to 5.3%, respectively).^{1,2} Less patients in the olaparib arm compared to the placebo arm had Stage IV disease (15.4% and 19.8%, respectively). Approximately, 25.4% (n=66) of patients in the olaparib arm had a BRCA2 mutation, which was approximately 5% less patients compared to the placebo arm (n=40; 30.5%). There were more patients in the olaparib arm with a BRCA1 mutation (n=191; 73.5%) compared to the placebo arm (n=91; 69.5%).¹

Efficacy

The key efficacy outcomes of SOLO1 are presented in Table 1.1 (data cut-off May 17th, 2018). The median duration of follow-up was 40.7 months (interquartile range: 34.9, 42.9) in the olaparib arm and 41.2 months (interquartile range: 32.2, 41.6) in the placebo arm.¹ The key primary (i.e., PFS) and secondary outcomes (i.e., PFS2, OS) that were controlled for multiplicity are summarized below. Additional secondary outcomes are presented in Table 1.1.

- Progression-free survival: A total of 198 investigator-assessed PD events or death occurred, with 102 (39.2%) in the olaparib arm and 96 (73.3%) in the placebo arm. There was a 70% reduction in the risk of PD or death in the olaparib arm compared to the placebo arm (HR: 0.30; 95% CI: 0.23, 0.41; p<0.001). All exploratory subgroup analyses demonstrated a statistically and clinically significant benefit with olaparib compared to placebo. Sensitivity analyses evaluating potential biases and using centrally confirmed germline and somatic BRCA mutated subsets of the study population were consistent with the primary analysis of PFS.^{1,2}
- Second progression-free survival: A total of 121 PFS2 events (time from randomisation to second PD or death event) occurred, with 69 (26.5%) in the olaparib arm and 52 (39.7%) in the placebo arm.^{1,2} There was a 50% reduction in the risk of second PD event or death in the olaparib arm compared to the placebo arm (HR: 0.50; 95% CI: 0.35, 0.72; p<0.001).¹
- Overall survival: At the time of the analysis, the interim OS data were immature (~21% maturity). A total of 82 deaths occurred, with 55 (21.2%) in the olaparib arm and 27 (20.6%) deaths in the placebo arm.^{1,2} There was no difference in the risk of death between the olaparib and placebo arms (HR: 0.95; 95% CI: 0.60, 1.53).¹

Quality of Life

Study compliance was high (>80%) from baseline to week 97.² Mean baseline trial outcome index (TOI) scores were similar between treatment arms. The adjusted mean change from baseline to 24 months was 0.3 (95% CI: -0.72, 1.32) in the olaparib arm and 3.3 (95% CI: 1.84, 4.76) in the placebo arm. The estimated difference between the treatment arms in mean change from baseline to 24 months was -3.00 (-4.78, -1.22), which was statistically, but determined to not be clinically, significant.¹

Safety

AEs of any grade occurred in 5% more patients in the olaparib arm (n=256; 98%) compared to the placebo arm (n=120; 92%), and serious adverse events (SAEs) occurred in 9% more patients in the olaparib arm (n=54; 21%) compared to the placebo arm (n=16; 12%).^{1,2} The proportion of patients with grade ≥3 AEs was 21% higher in the olaparib arm, occurring in 102 (39%) and 24 (18%) patients in the olaparib and placebo arms, respectively.¹

- Any grade AEs: The most commonly occurring any grade AEs in the olaparib arm included nausea (n=201; 77%), fatigue or asthenia (n=165; 63%), vomiting (n=104; 40%). The most common AEs (≥10% frequency) were known to occur with the use of olaparib, except for constipation (n=72; 28%), dyspnoea (n=39; 15%), and urinary

tract infections (n=31; 11.9%).⁸ In the placebo arm, the most common any grade AEs included fatigue or asthenia (n=54; 42%), nausea (n=49; 38%), and arthralgia (n=35; 27%).¹

- SAEs: Anemia was the most common SAE in the olaparib arm followed by urinary tract infection, which occurred in 17 (6.5%) and 3 (1.2%) patients, respectively, compared to no patients in the placebo arm. Breast cancer was the most common SAE in the placebo arm and occurred in 3 (2.3%) of patients compared to 1 (0.4%) of patients in the olaparib arm. Overall, new primary cancers occurred in 5 (2%) patients vs. 3 (2%) patients in the olaparib and placebo arms, respectively. In the olaparib arm, AML occurred in 3 (1%) patients, and pneumonitis or interstitial lung disease occurred in 5 (2%) patients, whereas no patients in the placebo arm experienced these SAEs.¹
- Withdrawals due to AEs (WDAEs): The proportion of patients who discontinued treatments due to AEs was 10% higher in the olaparib arm (n=30; 12%) compared to the placebo arm (n=3; 2%).¹
- Deaths: There were no deaths that occurred due to AEs while on study treatment and up to the 30 day follow-up period following treatment discontinuation. However, there were 4 deaths that occurred after this period in the olaparib arm that were not considered to be related to the disease under investigation. Two deaths occurred due to AML and one death due to septic shock, which were related to olaparib in the investigator's opinion. One death was an intentional overdose considered unrelated to olaparib.²

Table 1.1. Highlights of Key Outcomes

Primary Outcome (Investigator Assessed)	SOLO1	
	Olaparib (n=260)	Placebo (n=131)
Progression-free survival[†]		
Median, months (95% CI)	NR (NR, NR)	13.8 (11.1, 18.2)
HR (95%CI)	0.30 (0.23, 0.41)	
p-value [‡]	<0.0001	
Secondary Outcomes		
Second progression-free survival[†]		
Median, months (95% CI)	NR (NR, NR)	41.9 (36.5, 47.9)
HR (95% CI)	0.50 (0.35, 0.72)	
p-value [‡]	0.0002	
Overall survival		
Median, months (95% CI)	NR (NR, NR)	NR (NR, NR)
HR (95%CI)	0.95 (0.60, 1.53)	
p-value [‡]	0.8903	
Time to first subsequent therapy or death (TFST)^{††}		
Median, months (95% CI)	51.8 (44.3, NR)	15.1 (12.7, 20.5)
HR (95%CI)	0.30 (0.22, 0.40)	
p-value [‡]	<0.0001	
Time to second subsequent therapy or death (TSST)^{††}		
Median, months (95% CI)	NR (NR, NR)	40.7 (32.9, 47.7)
HR (95%CI)	0.45 (0.32, 0.63)	
p-value [‡]	<0.0001	
Time to study treatment discontinuation or death (TDT)^{††}		
Median, months (95% CI)	24.6 (24.0, 24.8)	13.8 (11.2, 16.4)
HR (95%CI)	0.63 (0.51, 0.79)	
p-value [‡]	<0.0001	
Time to earliest progression by RECIST 1.1, CA-125, or death^{††}		
Median, months (95% CI)	NR (NR, NR)	12.0 (10.8, 16.6)
HR (95%CI)	0.30 (0.23, 0.40)	

p-value [†]	<0.0001	
Overall response rate		
BOR (CR + PR), n (%)	23 (8.8)	6 (4.6)
Complete response	15 (5.8)	3 (2.3)
Partial response	8 (3.1)	3 (2.3)
Non-response (SD + PD + NE) n (%)	44 (16.9)	27 (20.6)
Stable disease ≥ 12 weeks	26 (10.0)	13 (9.9)
Progression	9 (3.5)	12 (9.2)
No evaluable follow-up assessments	9 (3.5)	2 (1.5)
HRQoL	Olaparib (n=260)	Placebo (n=131)
Change in Trial Outcome Index (based on FACT-O questionnaire)^{††}		
Mean score over 24 months (95% CI)	0.30 (-0.72, 1.32)	3.30 (1.84, 4.76)
Estimated difference between arms (95% CI)	-3.00 (-4.78, -1.22)	
p-value ^{††}	0.0010	
Harms Outcome, n (%)	Olaparib (n=260)	Placebo (n=130)
AEs (any grade)	256 (98.5%)	120 (92.3%)
Grade ≥3 AEs	102 (39.2%)	24 (18.5%)
Serious AEs	54 (20.8%)	16 (12.3%)
WDAEs	30 (11.5%)	3 (2.3%)
Fatal AEs ^{††}	0 (0%)	0 (0%)
Data cut-off date: May 17 th , 2018		
† Assessed using RECIST criteria		
* p-value is for the stratified log-rank test for the superiority of olaparib vs. placebo		
†† Secondary outcomes not controlled for multiplicity		
‡ No AEs with an outcome of death reported on study treatment or during the 30 day follow-up period. However, 4 deaths occurred after the 30 day follow-up, which included 2 patients in the olaparib arm with acute myeloid leukemia that resulted in death (related to olaparib), 1 patient with septic shock (related to olaparib), and 1 suicide (unrelated to olaparib).		
Abbreviations:		
AE = adverse event; CA-125 = cancer antigen 125; CI = confidence interval; CR = complete response; FACT-O = Functional Assessment of Cancer Therapy - Ovarian; HR = hazard ratio; HRQoL = health-related quality of life; NE = not evaluable; NR = not reached; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumours; SD = standard deviation; WDAE = withdrawal due to adverse event		
*HR < 1 favours olaparib		
Sources:		
EPAR, 2019		
Moore et al., 2018		
Clinicaltrials.gov		

Limitations

- There were a number of baseline characteristics that were imbalanced, which included cycles of first-line platinum-based treatment, international Federation of Gynecology and Obstetrics (FIGO) stage, and BRCA mutation. The combination of these imbalances may have confounded the results in an unknown direction.
- Though patients with germline or somatic mutations were eligible for participation in the study, almost all patient had a centrally confirmed germline BRCA 1/2 mutation, and thus the study results may not be generalizable to patients with only somatic BRCA mutations. In addition, the majority of patients had a serous histology with a primary tumor location in the ovary, and thus the study results may not be generalizable to endometrioid or other primary tumor locations (i.e., fallopian tube and primary peritoneal) included in the study.
- There were a larger proportion of patients that had a subsequent therapy in the placebo arm compared to the olaparib arm, with a higher proportion of patients in the placebo arm receiving a subsequent PARP inhibitor. The type and number of subsequent therapies received in each arm may have confounded the results in an unknown direction.

- Investigator-assessed outcomes were used for the primary analyses, which may be subject to bias. However, the amount of bias is considered minimal, as the submitter conducted sensitivity analyses using blinded independent central review (BICR) and the results were consistent with the investigator-assessed results.

1.2.2 Additional Evidence

See Section 3, Section 4, and Section 5 for a complete summary of patient advocacy group input, Provincial Advisory Group (PAG) Input, and Registered Clinician Input, respectively.

Patient Advocacy Group Input

One patient advocacy group, Ovarian Cancer Canada, provided input on olaparib as maintenance treatment after first line platinum-based chemotherapy for those with BRCA-mutated epithelial ovarian, fallopian tube or primary peritoneal cancer.

Ovarian Cancer Canada collected information from patients living with ovarian cancer and their caregivers through an anonymous online survey from March 25 to April 14, 2019. There was a total of 28 respondents, which included 25 people living with ovarian cancer and 3 caregivers. All respondents were Canadian, representing the Western and Central provinces of Canada (no respondents were from the territories or Atlantic Canada).

Respondents indicated that their lives were profoundly affected by ovarian cancer. The main identified challenges of ovarian cancer were work life, sexual relationship, physical activity, level of well-being, family/friend relationships, and sleep pattern. The current treatment is chemotherapy and surgery. Side effects of the current treatment include fatigue, hair loss, neuropathy, ascites, and blood problems. Commenters also described high levels of anxiety about the possibility of recurrence.

A total of 10 respondents indicated that they or those they were caregiving for had used olaparib as a treatment for ovarian cancer.

Almost all respondents believe that olaparib should be available as a treatment option after first line chemotherapy for women in Canada who have a BRCA gene mutation and ovarian cancer. They believe olaparib is a much-needed option for those with this type of cancer and has the potential to save lives.

Please see section 3 for a summary of specific input received from the patient advocacy groups.

Provincial Advisory Group (PAG) Input

The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.cadth.ca/pcodr). PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) and a federal drug plan participating in pCODR. PAG identified the following as factors that could be impact implementation of olaparib for newly diagnosed ovarian cancer:

Clinical factors:

- Eligible patient subpopulations
- Maximum time between completion of chemotherapy and olaparib initiation

Economic factors:

- Additional pharmacy, laboratory and nursing resources for dispensing and monitoring for adverse events (e.g., anemia)
- Clarity on treatment duration and criteria for discontinuation
- Resources for BRCA testing

Please see section 4 for a summary of specific input received from the patient advocacy groups.

Registered Clinician Input

Five clinician inputs were provided for olaparib for newly diagnosed ovarian cancer. Input was provided by three single clinicians, and two joint clinician inputs on behalf of Cancer Care Ontario (CCO) and the GOC. A summary of their input is provided below.

Current treatments available for patients include, monitoring as well as maintenance bevacizumab followed by chemotherapy. However, patients with known BRCA status were stated to undergo observation and are not usually given bevacizumab. Unmet need was highlighted by multiple clinicians, as currently there are no treatments for patients following initial therapy for ovarian cancer. Eligibility criteria from the SOLO-1 trial were agreed upon by all clinicians providing input as being applicable to current clinical practices. Extension of eligibility criteria to patients with evidence of homologous recombination deficiency (HRD) was also suggested by one clinician. Compared to bevacizumab, olaparib was stated to have a superior safety profile, was more tolerable, and was easier to administer. In terms of sequencing, all clinicians agreed olaparib should be used following completion of first-line treatment among patients exhibiting a clinical response. None of the clinicians agreed that olaparib should be provided to patients who received first-line bevacizumab due to the lack of available evidence showing efficacy. Clinicians had differing opinions about extending use of olaparib to patients with early stage disease, patients who received chemotherapy at an earlier stage of their ovarian cancer, patients who are not surgical candidates, or patients who are allergic or cannot tolerate platinum-based chemotherapy. Stopping rules for olaparib were suggested to include radiological progression of disease, and intolerance to olaparib. Treatment with olaparib was agreed upon by clinicians to begin within eight weeks of completing chemotherapy; however, clinicians identified that some circumstances might allow for patients to begin olaparib within an extended window of nine to twelve weeks. Somatic and germline testing were identified as relevant companion diagnostic testing required for receipt of olaparib. While both germline and somatic testing are evidence based and available, there were differing views by clinicians on preference of each test.

Please see section 5 below for a summary of specific input received from the registered clinicians.

Summary of Supplemental Questions

There were no supplemental questions identified for this review.

Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

1.2.3 Factors Related to Generalizability of the Evidence

Table 2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

Table 2: Assessment of generalizability of evidence for olaparib for advanced high-grade serous or endometrioid ovarian cancer, primary peritoneal cancer, or fallopian-tube cancer

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability																																																								
Population	ECOG PS	<p>The SOLO1 trial only included patients with ECOG PS 0-1.¹</p> <table border="1"> <thead> <tr> <th>ECOG PS</th> <th>Olaparib 260 (100%)</th> <th>Placebo 260 (100%)</th> </tr> </thead> <tbody> <tr> <td>0</td> <td>200 (77)</td> <td>105 (80)</td> </tr> <tr> <td>1</td> <td>60 (23)</td> <td>25 (19)</td> </tr> <tr> <td>Missing</td> <td>0 (0)</td> <td>1 (1)</td> </tr> </tbody> </table>	ECOG PS	Olaparib 260 (100%)	Placebo 260 (100%)	0	200 (77)	105 (80)	1	60 (23)	25 (19)	Missing	0 (0)	1 (1)	Do the results apply to ECOG PS ≥1?	The CGP agreed that patients with ECOG PS 0-2 would be reasonable candidates for olaparib, depending on the reasons why patient's performance status may be suboptimal and recovery from surgery/chemotherapy toxicities. These patients may potentially benefit from the convenient orally administered therapy with often manageable adverse side effects.																																												
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	Prior treatment with bevacizumab	<p>Patients treated with bevacizumab (either in combination or as maintenance therapy following combination) were excluded from the SOLO1 trial.¹</p>	<p>Would patients treated with bevacizumab during combination therapy in first line or as a maintenance therapy following first line therapy be eligible for olaparib?</p>	<p>The CGP feels that if a patient has been exposed to bevacizumab in the first line setting prior to the results of BRCA testing, it is reasonable to offer olaparib as sole maintenance therapy once patient is confirmed to have germline or somatic BRCA mutation.</p>																																																								

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
	Prior treatment for early stage disease	Patient who re-present with an advanced stage ovarian, fallopian tube, or primary peritoneal cancer were excluded from the SOLO1 trial. Only newly diagnosed patients with an advanced stage ovarian, fallopian tube, or primary peritoneal cancer were included in the trial. ¹	Would patients treated with chemotherapy (i.e., adjuvant) for a prior diagnosis with an earlier stage ovarian, fallopian tube, or primary peritoneal cancer be eligible for olaparib?	The CGP note that the SOLO1 evidence only provides evidence for newly diagnosed patients whose cancers are platinum-sensitive (complete or partial response to first-line platinum-based chemotherapy). The SOLO2 trial, previously reviewed by CADTH and approved for reimbursement, provides evidence supporting the use of olaparib after recurrent platinum-sensitive ovarian cancer, however, this indication is not a focus of this review.
	Non-surgical candidates	In the SOLO1 trial, patients with FIGO stage III disease must have had 1 attempt at optimal debulking surgery (upfront or interval debulking). FIGO stage IV patients must have had either a biopsy and/or upfront or interval debulking surgery. ¹	Would patients with FIGO Stage III or IV who are not surgical candidates be eligible for olaparib?	The CGP agreed that eligibility should be aligned to the SOLO 1 trial, mainly stage III patients who had an attempt at debulking surgery as well as stage IV patients with or without surgery.
	Response to prior therapy	Only patients with a complete response or partial response to first line platinum-based therapy were included in the SOLO1 trial. ¹	Would patients with stable disease be considered for maintenance therapy with olaparib?	The CGP consider that olaparib is still useful in platinum refractory ovarian cancer especially in patients with BRCA mutation. There is currently no evidence to guide the use of olaparib in patients who achieved stable disease (SD) and whether these patients will benefit from olaparib maintenance therapy. Therefore, olaparib is indicated for patients who achieved CR or PR by RECIST 1.1 (or GCIG). In patients who achieved SD, the CGP agree that although it is conceivable that these patients may benefit from olaparib maintenance therapy, further evidence is required before maintenance olaparib can be recommended in patients who achieve SD as best response.
	BRCA mutation	Patients with deleterious or suspected deleterious germline or somatic BRCA mutations were eligible for the study. As confirmed by central testing, 98% of patients	Are the results generalizable to patients with only somatic BRCA mutations?	The CGP agreed that regardless of germline or somatic, patients with BRCA mutation

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
		had a germline BRCA mutation (1.3% were missing). Two patients were determined to have BRCA wildtype and one patient with a BRCA variant of unknown significance. The two patients with BRCA wildtype were confirmed to have a somatic BRCA mutation from central review. A total of 82.9% of patients were confirmed to have a somatic BRCA mutation. ¹		should be eligible for olaparib maintenance therapy.
Intervention	Type of first-line therapy	In the SOLO1 trial, only patients with first-line platinum-based therapy were eligible for olaparib maintenance therapy. ¹	Would patients who have non-platinum-based chemotherapy due to a contraindication to platinum-based therapy (for example, patients who are allergic or unable to tolerate platinum-based chemotherapy), be eligible for maintenance with olaparib?	The consensus of the CGP was that BRCA positive patients who received platinum therapy but then received non-platinum based chemotherapy (due to intolerance) and had a response (and otherwise met the criteria for maintenance olaparib) should be candidates for olaparib. Given the difference in the mechanism of action of the agents, the CGP do not anticipate difference in response.
	Timing of olaparib	In the SOLO1 trial, olaparib maintenance therapy was initiated within 8 weeks of completion of platinum-based therapy for patients with a complete response or partial response to therapy. ¹	Would patients who completed platinum-based chemotherapy more than 8 weeks prior to the anticipated initiation of olaparib be eligible to receive olaparib? What would the maximum time between completion of chemotherapy and commencement of olaparib be?	The consensus of the CGP was that olaparib should be offered to all patients eligible for the first-line maintenance olaparib as long as the treatment can be started within 12 weeks of the last chemotherapy treatment, as multiple factors such as logistics and chemotherapy side effects can prevent some eligible patients from starting olaparib within 8 weeks as mandated in SOLO-1. If more than 8 weeks had elapsed from last chemotherapy treatment, consideration should be given to exclude disease progression before starting maintenance therapy (patients who have had disease progression should not be treated with olaparib maintenance).
	Treatment duration	In the SOLO1 trial, patients with no evidence of disease at 2 years were discontinued from treatment. Patients who experienced radiographical PD or patients who had evidence of disease that remained stable (no evidence of PD) could continue to receive treatment, if in the opinion of the investigator, it was in the patients' best interests. ¹ A total of 29 (7.4%) patients continued treatment beyond 2 years, with 26 (10%) patients in the olaparib arm and 3 (2.3%) in the placebo arm. Overall, 15 (5.8%) patients in the olaparib arm and 2 (1.5%) patients in the placebo arm	What criteria would be considered when treating patients beyond the 2-year maximum who have evidence of disease (for example, partial response or stable disease)?	The CGP recommended that olaparib be offered in the same fashion that was mandated in SOLO-1. Patients who had no evidence of disease at 2 years stopped receiving olaparib, but patients who had at least a partial response or stable disease at 2 years were permitted to continue receiving olaparib at the discretion of the treating oncologist.

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
		had stable disease, and continued treatment as per protocol criteria for continuing treatment beyond 2 years. There were 11 (4.2%) patients in the olaparib arm and 1 (0.8) patient in the placebo arm who continued treatment beyond 2 years in error, as these patients had no evidence of disease or a complete response at 2 years of olaparib maintenance therapy. ²		
	Disease assessment	In the SOLO1 trial, patients were to continue with study treatment until radiological PD, despite rises in CA-125 levels. Stopping rules included adverse events (unacceptable toxicities), severe non-compliance to study protocol, bone marrow findings consistent with MDS or AML, objective radiological PD as per RECIST criteria assessed by the investigator (unless continuation is justified due to clinical benefit), no evidence of disease at 2 years of treatment, and patient decision. Disease assessments by radiographical evaluation were conducted every 12 weeks (ie., 3 months) for the first 3 years, then every 24 weeks (ie., 6 months) until PD. ¹	How frequently should disease be assessed for patients on olaparib, as well as the stopping rules for olaparib (for example, rising CA-125 levels or a combination of CA-125 levels and radiological progression)?	The CGP notes that treatment is usually not stopped until CA 125 progression is confirmed by radiographical PD. Based on this the CGP agreed that the trial is consistent with clinical practice. Additionally, scans were conducted more frequently on the trial than in clinical practice. Although it may vary by center, in clinical practice, regular CA 125 and/or CT scans are recommended to monitor ongoing disease response and stability. CT scan may be typically conducted every 3 months for the first 2 years, every 4 months for the 3rd year, every 6 months for 4th-5th year, as clinically indicated.
	Dose interruptions and re-treatment	For the management of toxicities, dose interruptions were allowed as required for a maximum of 14 days per occasion. For longer interruptions, the sponsor was to be informed. ¹ Dose interruptions for patient preference were not explored in the SOLO1 trial.	For planned periods of dose interruptions due to patient preference during maintenance treatment, please provide guidance on re-treatment.	The CGP agreed that planned periods of dose interruptions due to patient preference should be allowed at the treating physician's discretion, not to exceed 1 month. A lack of cancer progression should be confirmed prior to restarting olaparib as maintenance therapy if the interruption is >14 days.
	Re-treatment after progression	Of patients who received a subsequent therapy in the olaparib arm, the most common regimen was platinum chemotherapy (n=58; 22.3%), followed by any other chemotherapy regimen (n=35, 13.5%). A total of 20 (7.7%) patients received a PARP inhibitor as a subsequent therapy, of which 13 patients received olaparib. ²	For patients who progress following completion of 2 years of olaparib maintenance therapy, would patients be treated with olaparib followed by second-line therapy for platinum-sensitive disease?	The CGP agreed that there is no evidence to support re-treatment with olaparib as maintenance therapy following second line therapy for platinum sensitive disease.
Comparator	Bevacizumab	Placebo was the comparator used in the SOLO1 trial. ¹ Bevacizumab in combination with carboplatin and paclitaxel in the first-line setting, and/or followed by bevacizumab maintenance therapy for platinum-sensitive patients, regardless of BRCA status, may be offered to a subset of patients with high-risk advanced stage epithelial ovarian cancer, fallopian tube, or primary peritoneal	In the absence of direct or indirect evidence comparing bevacizumab and olaparib as maintenance therapy following first-line treatment, is there a preference or criteria where	Input from registered clinicians as well as the CGP felt that a) patients who receive bevacizumab represent a small percentage of all patients receiving first-line treatment for advanced ovarian cancer; b) the availability of bevacizumab in the first-line setting is variable from province to province; c) if both

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
		cancer. However, since BRCA-mutated patients are a very specific and targeted population, indirect comparison to the literature available on bevacizumab was not deemed feasible by the clinical guidance panel and methods team since it was tested in a broader population. Direct comparison to bevacizumab was not tested in the SOLO1 trial.	one maintenance therapy would be used over the other in this setting?	options are available to patients with documented germline or somatic BRCA 1/2 positivity, the patient should be offered olaparib rather than bevacizumab. The CGP feels that if a patient has been exposed to bevacizumab in the first line setting prior to the results of BRCA, it is reasonable to offer olaparib as sole maintenance therapy to once patient is confirmed to have germline or somatic BRCA mutation.
Outcomes	Primary and secondary outcomes	The primary outcome for the SOLO1 trial was PFS by investigator assessment, and secondary outcomes included second PFS2 and OS. ¹ A sensitivity analysis was performed using BICR, which was consistent with the primary analyses by investigator assessment. Discordance between investigator and BICR assessment was 15%. ² Overall survival data were not mature (~21% maturity) at the time of analysis, and no difference was found between olaparib and placebo (HR: 0.95, 95% CI: 0.60, 1.53). ¹	Was the selection of PFS as assessed by investigators appropriate and justified for the primary analyses? In the absence of the final analysis of OS, which would provide a more objective measure of efficacy, is there confidence in the efficacy of olaparib using PFS?	The CGP agreed that PFS is an appropriate and justified primary endpoint in this setting and has been reflected upon in multiple other trials such as SOLO-2. While the final analysis of OS will be informative, a) the magnitude of PFS benefit in SOLO-1 is notable; b) a statistically significant OS benefit may be diluted by those who receive olaparib after recurrence.
Setting	Countries participating in the trial	The study was conducted in 118 sites across 15 countries including Canada. There were 31 Canadian patients that participated in the SOLO1 trial. ⁹	Are there known differences in the practice patterns between countries? Could these affect the applicability of the results to the Canadian population or implementation of olaparib in Canada?	In United States, Canada and Europe, even with some differences in the use of IP/IV chemotherapy and inclusion of bevacizumab, general practice patterns are quite comparable and the results of SOLO-1 are generalizable to Canadian patients.

Abbreviations:

AML = acute myeloid leukemia; BICR = blinded independent central review; BRCA = breast cancer gene; CA-125 = cancer antigen 125; ECOG PS = Eastern Cooperative Oncology Group Performance Status; FIGO = International Federation of Gynaecology and Obstetrics; HR = hazard ratio; MDS = myelodysplastic syndrome; OS = overall survival; PARP = polyadenosine 5' diphosphoribose polymerase; PD = progressive disease; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours

1.2.4 Interpretation

Ovarian cancer is the eighth leading cause of all deaths in Canadian women and fifth leading cause of cancer related death. The Canadian Cancer Society estimated that, in 2017, 2,800 women in Canada developed ovarian cancer, with 1,800 deaths due to this disease¹⁰. In patients with stage III or IV ovarian cancer, there is over 85% risk of relapse, at which point the cancer is considered incurable. Yet, since the addition of paclitaxel to standard therapy in the early 1990s and use of bevacizumab in a selected group of high-risk patients in the 2000s, there have been no major practice changing developments in ovarian cancer therapeutics and no significant improvement in survival had been observed over the past few decades. There is an urgent and significant unmet need for a new therapeutic option in ovarian cancer, particularly to prevent relapse and death.

Use of maintenance olaparib (a PARP Inhibitor) in advanced stage (FIGO Stage III-IV) ovarian, primary peritoneal, and/or fallopian tube cancers, with deleterious or suspected to be deleterious somatic or germline BRCA mutations, patients who are platinum-sensitive with demonstrated complete or partial response to first-line platinum-based chemotherapy has been shown to significantly improve progression-free survival compared with placebo (primary endpoint) in the SOLO-1 randomized controlled trial⁴. With the median follow-up of 40.7 months, PFS was not reached in the olaparib arm vs. 13.8 months in placebo arm (HR 0.30, 95% CI 0.23, 0.41, $p < 0.001$), with an unprecedented 70% reduction in risk of death or cancer progression. Mature data on overall survival are not yet available.

Serious adverse events (SAE) and grade ≥ 3 AEs were similar in both arms, with AEs of any grade occurring in 5% more patients in the olaparib arm (98.5% vs 92%). In particular, severe anemia (22% vs 2%), acute myeloid leukemia (2% vs 0.4%) and pneumonitis (2% vs 0%) were some of the serious side effects that occurred more often in olaparib arm than in placebo. This should be noted and patients appropriately informed and monitored. No death due to AE has occurred while on study treatment and up to the 30-day follow-up period following treatment discontinuation. There were four deaths that occurred after this period in the olaparib arm that were not considered to be related to the disease under investigation (3 of which may be related to olaparib).

Quality of life was measured based on FACT-O questionnaire. The mean Trial Outcome Index score at baseline was 73.6 in the olaparib group and 75.0 in the placebo group. The score remained stable in the olaparib group (237 patients), with an adjusted mean change from baseline to 2 years of 0.30 points (95% CI, -0.72 to 1.32), as compared with a change of 3.30 points (95% CI, 1.84 to 4.76) in the placebo group (125 patients). The estimated between-group difference in change was -3.00 points (95% CI, -4.78 to -1.22); while being statistically significant, the difference was not considered to be clinically meaningful.

Input from patient advocacy group indicated that the disease burden and its impact on day-to-day life were substantial. Individual comments as well as scored questions expressed a willingness to accept side effects from olaparib in exchange for prolonged progression free life from most of the patients. Benefits outweighed the risks was reported for 10 of the 14 respondents. Of note, a total of 10 respondents indicated that either themselves or those they were caregiving for had used olaparib as a treatment for ovarian cancer. Input from registered clinicians indicated that olaparib should be integrated into clinical practice.

1.3 Conclusions

The Clinical Guidance Panel concludes that there is a clear overall net clinical benefit to extending progression free survival using maintenance olaparib with favorable toxicity profile in patients with platinum-sensitive (complete or partial response to first-line platinum-based

chemotherapy) advanced (FIGO Stage III-IV) stage ovarian, primary peritoneal, and/or fallopian tube cancer patients with somatic or germline BRCA mutations that were deleterious or suspected to be deleterious based on one randomized phase III study (SOLO-1).

In making this conclusion, the CGP also considered the following:

- The CGP felt that patients of ECOG PS 0-2 would be reasonable candidates for olaparib in real-world setting and may potentially benefit from the convenient orally administered therapy with often manageable adverse side effects;
- Regarding the eligibility of patients with non-serous histology type, the CGP felt that all histologies with BRCA 1 or 2 mutation (germline or somatic) should be included for treatment;
- The CGP felt that while some cases of early stage disease may benefit from olaparib, the recommendation for the therapy should be limited to patients with stage III/IV disease consistent with the inclusion criteria of the SOLO 1 trial;
- No level I evidence exists for patients who have received bevacizumab. Input from registered clinicians as well as the CGP felt that a) patients who receive bevacizumab represent a small percentage of all patients receiving first-line treatment for advanced ovarian cancer; b) the availability of bevacizumab in the first-line setting is variable from province to province; c) if both options are available to patients with documented germline or somatic BRCA 1/2 positivity, the patient should be offered olaparib rather than bevacizumab;
- For patients who have had prior treatment for early stage disease, evidence suggests that BRCA positive patients would benefit from maintenance olaparib after recurrent platinum-sensitive ovarian cancer, based on SOLO-2, however, this indication is not a focus of this review;
- For patients who are not surgical candidates, the consensus of the CGP was that stage III patients who had debulking surgery as well as stage IV patients with or without surgery would be candidates for olaparib, according to SOLO-1;
- Patients with somatic BRCA mutations were included in SOLO-1. There is a biological basis for response to olaparib for these patients, and the CGP felt that they should be included in candidates for maintenance therapy;
- The consensus of the CGP was that BRCA positive patients who received platinum therapy but then received non-platinum based chemotherapy (due to intolerance) and had a response (and otherwise met the criteria for maintenance olaparib) should be candidates for olaparib;
- The consensus of the CGP was that olaparib should be offered to all patients eligible for the first-line maintenance olaparib as long as the treatment can be started within 12 weeks of the last chemotherapy treatment, as multiple factors such as logistics and chemotherapy side effects can prevent some eligible patients from starting olaparib within 8 weeks as mandated in SOLO-1. If more than 8 weeks had elapsed from last chemotherapy treatment, consideration should be given to exclude disease progression before starting maintenance therapy (patients who have had disease progression should not be treated with olaparib maintenance).
- The CGP recommended that olaparib be offered in the same fashion that was mandated in SOLO-1. Patients who had no evidence of disease at 2 years stopped receiving olaparib, but patients who had a partial response or stable disease at 2 years were permitted to continue receiving olaparib at the discretion of the treating oncologist.
- Regarding how the companion diagnostic germline and somatic BRCA tests will be implemented, currently each province has variable pathways for BRCA testing. For both germline and somatic; the availability and timeliness of testing are also variable and heterogeneous. The CGP recommends that each provincial health authorities facilitate timely BRCA testing pathways for all patients with advanced ovarian, fallopian tube and primary peritoneal cancers for both somatic and germline mutations.
- The CGP agreed with registered clinician input that for patients who progress on olaparib, subsequent treatment will be based on time from last chemotherapy, toxicity to prior therapies, and patient preference.

2 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Genitourinary Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

2.1 Description of the Condition

Epithelial ovarian cancer (EOC) comprises a heterogeneous group of epithelial malignancies arising from ovaries, fallopian tubes or peritoneum. EOC is the seventh most common cancer and the eighth leading cause of cancer death among women ¹¹. Unfortunately, because of delayed presentation and diagnosis, almost 70% of women with ovarian cancer are diagnosed in the later stage of disease (III/IV), and these women have particularly poor outcomes. Approximately 90% of ovarian tumors are surface epithelial in origin, and the papillary serous histology subtype accounts for approximately 75%, of which the large majority (70%) is high-grade. The site of origin of EOC remains unclear. Some studies suggest that serous EOC and primary peritoneal cancer (PPC) arise from the fallopian tube epithelium; however, other studies suggest an origin within stem cells of the ovarian surface epithelium. EOC, PPC and fallopian tube cancer (FTC) behave very similarly and are therefore treated in the same way. In Canada, 2,800 women were diagnosed with ovarian cancer in 2017, and 1,800 died of this disease ¹².

It is now well recognized that 25-30% of patients with ovarian cancer have either a pathogenic germline (inherited) or somatic (limited to the tumour) mutation in *BRCA1* or *BRCA2* irrespective of family history ¹³⁻¹⁵. *BRCA1* and *BRCA2* genes are human tumour suppressor genes and a key component in homologous recombination (HR), a repair pathway of double-stranded DNA breaks ¹⁶⁻¹⁸. HR deficiency (HRD) such as pathogenic *BRCA* mutations causes cells to repair via less precise and more error-prone repair pathways such as non-homologous end-joining (NHEJ); inhibition of poly (ADP-ribose) polymerase (PARP) can confer synthetic lethality in cells with HRD ¹⁹. It is estimated that approximately 50% of high grade serous ovarian carcinomas (the most common but lethal ovarian cancer) have aberrations in HR repair pathways ²⁰.

Because of this association between ovarian cancer and *BRCA* mutations, these women are eligible for genetic testing, which has important downstream implications for family members, who can undergo hereditary screening, risk management, and importantly, potentially therapeutic options. It is also important because recently, PARP inhibitors have emerged as an effective therapeutic strategy in ovarian cancer, particularly for those with germline or somatic pathogenic *BRCA* mutations. Multiple phase 2 and 3 studies have previously demonstrated a significantly prolonged progression-free survival in patients with recurrent platinum-sensitive ovarian cancer and presence of germline or somatic *BRCA* mutations, as well as in patients with or without other HRD ²¹⁻²⁷.

2.2 Accepted Clinical Practice

Standard of care treatment for newly diagnosed ovarian cancer involves cytoreductive surgery and platinum-based systemic therapy (most often carboplatin/paclitaxel Q3week) ²⁸. Ideally, patients receive cytoreductive surgery followed by chemotherapy with carboplatin and paclitaxel (CP) (IP/IV) ²⁸. In patients who are not candidates for upfront cytoreductive surgery, IV CP followed by surgery if feasible then further CP are offered. In some patients, surgery is not possible at any point and patients receive CP only ²⁸. There is evidence that patients defined as “high-risk” (suboptimally debulked stage III or stage IV patients who may or may not be a candidate for surgery) will obtain potential OS and PFS benefit from first-line carboplatin/paclitaxel with upfront and maintenance bevacizumab ²⁹. However, the evidence

is somewhat conflicting in regards to which subgroup truly benefits from the addition of bevacizumab ³⁰, and therefore the addition of bevacizumab is not universally available as a publicly funded treatment option across Canada.

After first-line chemotherapy +/- surgery is finished, patients are followed-up every 3-6 months with history and physical examination. No routine regular imaging studies or bloodwork in asymptomatic patients have been shown to reliably improve survival and thus is not recommended ³¹. Most of the recurrences are detected by patient reporting of symptoms.

Surgery and systemic therapy are often successful in achieving tumour response, but with a high rate of relapse especially in patients with advanced-stage cancer (Fédération Internationale de Gynécologie et d'Obstétrique or FIGO stages III-IV) ³². Despite best efforts, more than 80% of patients with stage III-IV ovarian cancer, and almost everyone who has suboptimal debulking or no debulking, relapse/progress with incurable cancer. At recurrence, patients are treated with a variety of systemic therapy options, but with the understanding that the cancer is incurable and a prognosis in the range of 2-3 years.

NCCN ³³ and ESMO ²⁸ guidelines are some of the widely accepted international guidelines for investigations and management of EOC, include in Canada; however, practices across the provinces may vary depending on the provincial guidelines as well.

2.3 Evidence-Based Considerations for a Funding Population

The patient population of interest for this reimbursement request consists of patients with advanced stage (FIGO Stage III-IV) ovarian, primary peritoneal, and/or fallopian tube cancers, with deleterious or suspected to be deleterious somatic or germline BRCA mutations, and platinum-sensitive with demonstrated complete or partial response to first-line chemotherapy. Companion diagnostic tests in consideration include germline BRCA 1 and 2 testing as well as BRCA mutation tests on tumour specimens.

2.4 Other Patient Populations in Whom the Drug May Be Used

The drug olaparib is already approved for use in patients with relapsed platinum-sensitive ovarian, primary peritoneal, and/or fallopian tube cancers who have completed chemotherapy after relapse. Olaparib is also being actively investigated in many ongoing clinical trials including its use in combination with chemotherapy to achieve better clinical response, in combination with other anti angiogenic or immunomodulatory agents to increase the effectiveness of olaparib in a broader patient population, and prevention of PARPi resistance (non-BRCA populations)³⁴⁻³⁷.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

One patient advocacy group, Ovarian Cancer Canada, provided input on olaparib as maintenance treatment after first line platinum-based chemotherapy for those with BRCA-mutated epithelial ovarian, fallopian tube or primary peritoneal cancer.

Ovarian Cancer Canada collected information from patients living with ovarian cancer and their caregivers through an anonymous online survey from March 25 to April 14, 2019. Patients were included if they: 1) were diagnosed with epithelial ovarian, fallopian tube or primary peritoneal cancer and; 2) had been treated with platinum-based chemotherapy and; 3) had not had a recurrence of ovarian cancer and; 4) tested positive for a BRCA gene mutation and; 5) had or had not taken olaparib as a treatment for their ovarian cancer. The survey was promoted through Ovarian Cancer Canada's database, social media and partners.

There was a total of 28 respondents, which included 25 people living with ovarian cancer and 3 caregivers. Ovarian Cancer Canada noted that some respondents chose to skip questions. All respondents were Canadian, representing the Western and Central provinces of Canada (no respondents were from the territories or Atlantic Canada). The age of patients varied from 31-71 years, with most being aged 50-60 (n=9) or 60-70 (n=11) years. Fewer patients were under 40 (n=1), aged 40-50 (n=2) or over 70 (n=2). 22 patients had been diagnosed between 2013-18 (88%), while 3 were diagnosed between 2011-12 (12%). Most respondents had been diagnosed at stage III or IV (n=25; 89%). Respondents living with ovarian cancer included those diagnosed with epithelial ovarian cancer (n=15), primary peritoneal cancer (n=3), fallopian tube cancer (n=2), and five (n=5) respondents did not know the type of ovarian cancer. Of the 28 respondents, 16 had a BRCA2 gene mutation, 11 had a BRCA1 mutation and 1 did not know the type of mutation.

Respondents indicated that their lives were profoundly affected by ovarian cancer. The main identified challenges of ovarian cancer were work life, sexual relationship, physical activity, level of well-being, family/friend relationships, and sleep pattern. The current treatment is chemotherapy and surgery. Side effects of the current treatment include fatigue, hair loss, neuropathy, ascites, and blood problems. Commenters also described high levels of anxiety about the possibility of recurrence.

A total of 10 respondents indicated that they or those they were caregiving for had used olaparib as a treatment for ovarian cancer.

Almost all respondents believe that olaparib should be available as a treatment option after first line chemotherapy for women in Canada who have a BRCA gene mutation and ovarian cancer. They believe olaparib is a much-needed option for those with this type of cancer and has the potential to save lives. Please see below for a summary of specific input received from the patient advocacy groups.

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with Ovarian Cancer

Survey respondents indicated that ovarian cancer profoundly affected their lives. Respondents were asked to rate the impact of ovarian cancer of different areas of life from 1 (no effect) to 5 (extremely negative). Of the 25 respondents to this question, the key areas of concern (rated 4 or 5 on the scale) were identified as: work life (n=11; 44%), sexual relationship (n=11; 44%), physical activity (n=10; 40%), level of well-being (n=9; 36%), family/friend relationships (n=8; 32%), and sleep pattern (n=7; 28%).

Respondents described physical and emotional challenges, including: lack of energy, financial loss, inability to work or be physically active, and a negative impact on sexual health. There were also comments on the fear of recurrence, death and their levels of

anxiety and worry. Ovarian Cancer Canada noted that for patients diagnosed at stage III or IV, there is a 65-95% chance of recurrence, and thus it was not unexpected that patients reported high levels of stress and anxiety due to fear of this high chance of recurrence.

Patients described their experience in their own words:

- “Ovarian cancer has affected my life physically, emotionally and spiritually. Physical limitations after chemo make it difficult to care for my spouse’s meals. Difficult to work and difficult due to weakness to care for myself. Emotionally off balance because I cannot do the things I want to do because I am so unwell.”
- “My physical activity is close to where it was, including downhill skiing, hiking, and other active pursuits....The worst impact for me has been on my sex life with my husband - by the time we tried to resume it, almost a year after treatment, it was too painful. I have tried some suppositories recommended by the oncologist and they might provide a little benefit but not enough. We have pretty well given up trying.”
- “I had to stop working; financial loss; may need to sell home; lack of energy; self-esteem; sleep and appetite affected.”
- “I find with this cancer that my anxiety levels are high. You always worry about a recurrence and the rate of recurrence is very high with ovarian cancer. I have more difficulty in planning future events. I try to enjoy more the moment.”
- “Each follow-up appointment during my remission was stressful because I knew that the recurrence was high.”

3.1.2 Patients’ Experiences with Current Therapy for Ovarian Cancer

All respondents and caregivers reported that the current treatments included chemotherapy and surgery. The order of treatments was as follows: surgery then chemotherapy (n=11; 39%), chemotherapy then surgery then more chemotherapy (n=11; 39%), chemotherapy then surgery (n=3; 11%), no surgery (n=3; 11%).

In response to the survey question “Please rate the extent to which you agree or disagree with the following statement: ‘My initial treatments (not including Olaparib) are (were) able to manage my ovarian cancer,’” 23 of 28 (82%) respondents strongly agreed. Respondents continued to express the fear of remission, similar to as described in section 3.1.1, and in the words of one patient, “I’m blessed to be in remission. I try to remain positive and continue with a normal life but the thoughts of recurrence are constantly on my mind.”

There was an overall negative effect of current treatment on those diagnosed with ovarian cancer. When asked to rate the effects of treatment on a scale from 1 (no effect) to 5 (extremely negative effect), of the 28 patients that responded to this question, the following areas were identified as very negative or extremely negative: fatigue (n=13; 46%), hair loss (n=13; 46%), neuropathy (n=10; 36%), ascites (n=7; 25%), blood problems (n=7; 25%). Side effects rated as minimal or no effect included loss of fertility, skin irritation, nausea/vomiting, ascites, and bowel problems. Patients described their experiences with side effects as follows:

- “I still have the sensation of a lump under my feet so very difficult to walk for very long and hard to find adequate shoes.”
- “The treatment (chemotherapy) left me with peripheral neuropathy and balance is affected. I have not returned to the same high level of physical fitness as before.”

- “It was a seven-month ordeal during treatment but since I've gotten steadily stronger and am back working.”
- “My main issue has been the tiredness but I try my best to keep life as normal as possible.”

Respondents were asked to rate how much specific barriers impacted their access to treatment. Of the 24 patients that answered this question, the most significant barriers were travel issues (n=4; 17%), financial issues (n=4; 17%) and treatment not available (n=1; 4%). Comments described having to relocate, secure or pay for transportation, pay for products or home care, and fight for access to a certain treatment.

3.1.3 Impact of Ovarian Cancer and Current Therapy on Caregivers

The three caregiver respondents consisted of 1 other family member, 1 friend, and 1 private duty health care provider. Two caregivers have been providing care for less than 1 year and one caregiver has been providing care for between 1-2 years. Caregivers provided 1-3 hours (1), 6-12 hours (1) and more than 12 hours (1) of care per day. The two issues most negatively impacted were family relationships and the caregiver's ability to care for their family. One caregiver described, “I have young children. The need to care for my cousin who is unmarried and does not live close to me has resulted in me spending a few days away to look after her after she had her chemotherapy. This took me away from attending key children events.”

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for and Experiences To Date with Olaparib

Respondents were asked to rate the importance of certain issues if they were to take olaparib. The following issues were rated as high or extremely important by 16 respondents (57%) that answered this question : prolong their survival (n=16; 100%), lengthen time until recurrence (n=16; 100%), improve their quality of life (n=14; 88%), reduce visits to the cancer centre (n=11; 69%).

Sixteen respondents (57%) answered the following question: “On a scale of 1 (no improvement) to 5 (no sign of cancer), how much improvement in your ovarian cancer would you need to see before you would consider taking Olaparib”, over half (n=10; 63%) of the sixteen respondents indicated they would be willing to take Olaparib if there was no improvement, or mild or moderate improvement (score of 1-3 out of 5) in their ovarian cancer.

Of the 16 respondents, many would be willing to tolerate many side effects if olaparib were to improve their overall daily functioning or prognosis. Side effects rated most tolerable were tiredness (n=14; 88%), taste changes (n=11; 69%), nausea (n=9; 56%), bruising and bleeding easily (n=7; 44%), and headaches (n=7; 44%). Blood disorders or blood cancer and inflammation of lungs were those side effects least willing to be tolerated. One individual described the side effects as similar to those of chemotherapy.

Several individual comments expressed a willingness to accept side effects in exchange for prolonged life, described as a “small price to pay in exchange for life!” by one individual. Benefits outweighed the risks for 10 of 14 respondents (71%); 3 (21%) were not sure and 1 (7%) thought benefits did not outweigh risks

According to sixteen respondents, 75% (n=12) indicated the greatest benefits of taking olaparib would be: increasing the length of time before recurrence (n=7; 44%) and prolonging life (n=5; 31%). Improved quality of life (n=2; 13%) was also reported as a

benefit of taking olaparib. Nine respondents (56%) were not sure about potential risks, and 4 (25%) considered side effects to be risks.

Seven patients and three caregivers had direct experience with olaparib as treatment for ovarian cancer. One respondent had to discontinue olaparib due to low haemoglobin and has not received any further treatment.

The top two issues that olaparib managed or managed better than previous treatments were: 1) prolonged survival and 2) lengthened time to recurrence; followed closely by reduced visits to the cancer centre, shrinking tumour size, and improved quality of life.

Nine respondents agreed or strongly agreed that olaparib improved their quality of life compared to previous treatments used. Improved quality of life was described by patients as feeling physically well, hope/opportunity to extend life, and having increased peace of mind about recurrence as a result of olaparib. One patient also commented on the mode of administration of olaparib as “easier than chemotherapy regimen”. Caregivers also noted improved quality of life and reduced fear of recurrence in those they care for. One caregiver noted the financial burden they faced taking olaparib given the lack of coverage for this indication.

Nine respondents reported side effects from olaparib, which included tiredness/weakness (n=5), blood problems (n=3), and dry mouth (n=2). Three respondents reported they had no side effects. One respondent said that all side effects would be acceptable if the drug could improve their overall daily functioning or prognosis. Two respondents listed blood problems as an unacceptable side effect.

3.3 Additional Information

Ovarian Cancer Canada provided additional information about the impact of genetic testing on this population. Of the 28 respondents, 22 (79%) were recommended for genetic testing by a physician, 2 (7%) were recommended by family members, and 4 (14%) sought out testing individually. Three individuals also paid for the testing themselves, while the respective health systems paid for the remainder. Ovarian Cancer Canada suggested that if BRCA-positive patients are not qualifying for testing under current health system eligibility requirements and have sought testing for themselves and were found to be BRCA mutated, there may be more people who can benefit from olaparib than are being identified.

Most respondents were tested at the time of surgery (55%), whereas 22% were not tested and 22% did not know. Some respondents indicated they tested negative for a germline BRCA mutation but were positive for somatic BRCA mutations. Most respondents were satisfied with genetic testing, and the greatest negative impact of testing for both patients and caregivers was anxiety, although it was only rated as highly or extremely negative by 18% (n=5) of respondents. The length of wait time for results and that testing delayed treatment were also negative impacts, however rated as highly or extremely negative by 7% (n=2) of 28 respondents.

Respondents described the impact of genetic testing on their family, in terms of explaining family histories of cancer, as well as informing family members of important medical information so they could take protective measures for their own health.

Almost all respondents (96%) believed olaparib should be available as a treatment option after first line chemotherapy for woman in Canada who have a BRCA mutation and have ovarian cancer. Of those in favour of olaparib, respondents commented:

- “It is ridiculous that this drug is not made available for everyone. I have chosen to accept the financial burden but am fortunate that I am able to do so.”

- “If it can possibly prolong your life and keep your disease under control it should be available. Ovarian cancer does not have many new treatment options.”
- “Absolutely believe it is of benefit and should be covered for this indication. Her physician has recommended it for this indication, so there is no reason why Canadian women should not have the same access to this life saving medicine as women in other countries.”

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.cadth.ca/pcodr). PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) and a federal drug plan participating in pCODR. PAG identified the following as factors that could be impact implementation of olaparib for newly diagnosed ovarian cancer:

Clinical factors:

- Eligible patient subpopulations
- Maximum time between completion of chemotherapy and olaparib initiation

Economic factors:

- Additional pharmacy, laboratory and nursing resources for dispensing and monitoring for adverse events (e.g., anemia)
- Clarity on treatment duration and criteria for discontinuation
- Resources for BRCA testing

Please see below for more details.

4.1 Factors Related to Comparators

PAG identified that monitoring and maintenance bevacizumab is the standard of care following platinum-based chemotherapy (e.g., bevacizumab in combination with paclitaxel and carboplatin) for these patients. The comparator in SOLO-1 trial was placebo, PAG is seeking comparative data on olaparib compared to bevacizumab.

4.2 Eligible Patient Population

PAG is seeking guidance on whether the following subgroups of patients would be eligible for treatment with olaparib, as they were excluded in the SOLO-1 trial:

- Patients who received bevacizumab during their first-line course of treatment, either in combination or as maintenance therapy following combination therapy
- Patients with early stage disease (FIGO Stage I, IIA, IIB or IIC)
- Patients who have previously received chemotherapy (i.e., adjuvant) for prior diagnosis at an earlier stage for their ovarian, fallopian tube or primary peritoneal cancer
- Patients who are not surgical candidates, in the trial stage III patients must have had one attempt at optimal debulking surgery (upfront or interval debulking) and stage IV patients must have had either a biopsy and/or upfront or interval debulking surgery

There is a small number of patients who may be allergic to or unable to tolerate platinum-based chemotherapy, and therefore would have non-platinum therapy. PAG is seeking guidance on whether olaparib following first-line non-platinum-based chemotherapy is appropriate.

In the SOLO-1 trial, treatment with olaparib started within 8 weeks of their last dose of chemotherapy. PAG is seeking guidance on whether olaparib could be considered for patients who have completed platinum based chemotherapy more than eight weeks ago and what maximum time between completion of chemotherapy and commencement of olaparib would be.

If recommended for reimbursement, patients currently being monitored or on maintenance bevacizumab following first-line chemotherapy (e.g., bevacizumab with chemotherapy), would need to be addressed on a time-limited basis.

PAG has concerns for indication creep for patients who progressed or had stable disease on first-line platinum-based chemotherapy (i.e., did not have complete response or partial response) and patients who do not have a BRCA mutation. PAG noted these patients would be out of scope of this review.

4.3 Implementation Factors

Olaparib is available in 100 and 150 mg tablets and tablet availability minimizes pill burden, this is an enabler to implementation. However, drug wastage will occur with dose modifications from 150 mg to 100 mg tablets.

PAG noted that olaparib would be additional therapy as it is maintenance therapy and does not replace chemotherapy. Extra pharmacy, laboratory, and nursing resources for dispensing and monitoring would be required, as patients would otherwise be on observation. Additional blood work for monitoring anemia and blood transfusions for severe anemia may be required. PAG has concerns that the high rate of grade 3 and 4 anemia could impact quality of life significantly at this stage of disease and would require resources to manage. PAG also noted that the risks of developing Myelodysplastic syndrome/Acute Myeloid Leukemia and pneumonitis are not insignificant and additional resources would be required to monitor monthly and treat these serious adverse event.

PAG is seeking clarity on treatment duration (i.e., two year maximum, if not the criteria to determine if treatment should go beyond) and monitoring of disease. In the SOLO-1 trial, patients could continue treatment for two years or until disease progression. However, patients who had evidence of stable disease at two years could continue to receive olaparib, if in the opinion of the investigator, it was in the patient's best interest. If at two years the patient had evidence of disease, the treatment was to be discontinued. PAG is also seeking clarity on how frequently disease should be assessed on olaparib and what the stopping rules are for olaparib (e.g., rising CA-125 levels or combination of rising CA-125 levels and radiological progression). PAG is seeking guidance on re-treatment with olaparib following periods of planned treatment interruption due to patient preference during maintenance treatment.

PAG noted that olaparib is an oral drug that can be delivered to patients more easily than intravenous therapy in both rural and urban settings, where patients can take oral drugs at home, and no chemotherapy chair time would be required. PAG identified the oral route of administration is an enabler to implementation.

However, in some jurisdictions, oral medications are not funded in the same mechanism as intravenous cancer medications. This may limit accessibility of treatment for patients in these jurisdictions as they would first require an application to their pharmacare program and these programs can be associated with co-payments and deductibles, which may cause financial burden on patients and their families. The other coverage options in those

jurisdictions which fund oral and intravenous cancer medications differently are: private insurance coverage or full out-of-pocket expenses.

4.4 Sequencing and Priority of Treatment

For patients who receive olaparib monotherapy maintenance in this setting and then develop metastatic disease,

- What treatments can they receive and how should these treatments be sequenced (e.g., use of platinum-based chemotherapy)?
- For patients who complete two years of olaparib monotherapy maintenance and then progress, would patients be treated with olaparib followed by second-line platinum-based chemotherapy (e.g., as second-line treatment for platinum-sensitive disease, as per the previous pERC recommendation for olaparib as monotherapy maintenance treatment of adult patients with platinum-sensitive relapsed BRCA-mutated epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response to platinum-based chemotherapy)?

4.5 Companion Diagnostic Testing

BRCA testing is already in place in some provinces for ovarian cancer but not at time of diagnosis, there will be costs associated with the BRCA testing as BRCA mutation is not routinely tested at this time. In addition, PAG noted that the BRCA test results can take a long time and there would be a delay in the initiation of treatment from completion of platinum-based chemotherapy. Turn-around time would need to be completed in a sufficient time as treatment would need to start within 8 weeks of completing chemotherapy.

In the SOLO-1 trial, eligible patients had a deleterious or suspected deleterious germline or somatic BRCA1/2 mutation. PAG is seeking guidance on the definitions of deleterious BRCA mutations as well as whether BRCA testing can be somatic or germline.

PAG noted that there will be a large number of patients requiring BRCA testing to identify patients who would be eligible for treatment with olaparib. This adds tremendous strain to limited resources in genetic testing.

4.6 Additional Information

None.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

Five clinician inputs were provided for olaparib for newly diagnosed ovarian cancer. Input was provided by three single clinicians, and two joint clinician inputs on behalf of Cancer Care Ontario (CCO) and the GOC. A summary of their input is provided below.

Current treatments available for patients include, monitoring as well as maintenance bevacizumab followed by chemotherapy. However, patients with known BRCA status were stated to undergo observation and are not usually given bevacizumab. Unmet need was highlighted by multiple clinicians, as currently there are no treatments for patients following initial therapy for ovarian cancer. Eligibility criteria from the SOLO-1 trial were agreed upon by all clinicians providing input as being applicable to current clinical practices. Extension of eligibility criteria to patients with evidence of homologous recombination deficiency (HRD) was also suggested by one clinician. Compared to bevacizumab, olaparib was stated to have a superior safety profile, was more tolerable, and was easier to administer. In terms of sequencing, all clinicians agreed olaparib should be used following completion of first-line treatment among patients exhibiting a clinical response. None of the clinicians agreed that olaparib should be provided to patients who received first-line bevacizumab due to the lack of available evidence showing efficacy. Clinicians had differing opinions about extending use of olaparib to patients with early stage disease, patients who received chemotherapy at an earlier stage of their ovarian cancer, patients who are not surgical candidates, or patients who are allergic or cannot tolerate platinum-based chemotherapy. Stopping rules for olaparib were suggested to include radiological progression of disease, and intolerance to olaparib. Treatment with olaparib was agreed upon by clinicians to begin within eight weeks of completing chemotherapy; however, clinicians identified that some circumstances might allow for patients to begin olaparib within an extended window of nine to twelve weeks. Somatic and germline testing were identified as relevant companion diagnostic testing required for receipt of olaparib. While both germline and somatic testing are evidence based and available, there were differing views by clinicians on preference of each test.

Please see below for a summary of specific input received from the registered clinicians.

5.1 Current Treatment(s) for Newly Diagnosed Ovarian Cancer

The following treatments for patients with newly diagnosed ovarian cancer were acknowledged identified by PAG: monitoring and maintenance bevacizumab as standard of care following platinum-based chemotherapy, for example bevacizumab in combination with paclitaxel and carboplatin. One of the individual clinicians and one joint clinician input agreed with these treatments as current treatments for patients with newly diagnosed ovarian cancer. Further details were provided by another joint clinician input, stating that observation is the standard of care for patients following primary treatment usually with platinum-taxol doublet chemotherapy, or maintenance bevacizumab for patients with high risk disease, defined as stage III sub-optimally debulked, or stage III unresectable, or stage IV patients.

One of the individual clinicians stated that many centres currently do not offer bevacizumab for patients with known BRCA mutation status; these patients are instead monitored. Another clinician highlighted the unmet need for these patients, as women with ovarian cancer who complete initial treatment do not have other treatment options available to them. The clinician stated that oncologists do an excellent job at reducing burden of disease during the initial treatment phase, however over 80% of patients will recur.

5.2 Eligible Patient Population

All clinicians agreed that the patient population in the reimbursement request, and the inclusion and exclusion criteria of the trial were applicable to clinical practice. One clinician also stated that patients with mutations in BRCA 1 or 2 account for approximately 25% of patients with advanced ovarian cancer. A gap in treatment for all ovarian cancer patients after initial treatment was also acknowledged. An individual clinician stated that strong data exists to support the use of olaparib as monotherapy for the maintenance treatment of adults with advanced BRCA-mutated high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy. One clinician suggested extending the indication to patients showing evidence of HRD.

5.3 Relevance to Clinical Practice

Olaparib was stated to be highly effective and should be offered to all women with mutations in BRCA 1 or 2 upon completion of initial treatment of ovarian cancer. Unmet need was highlighted by many clinicians for patients in this setting. Multiple clinicians identified that there is currently no other therapy that provides the same survival improvement for patients. The results of the SOLO-1 trial were described by one clinician as being the most significant finding in the management of ovarian cancer since the discovery of platinum-based treatments. Further, the clinician stated that the results of the SOLO-1 trial are practice changing, as the current median survival for women with stage III or IV ovarian cancer is approximately 3.5 years.

Olaparib was stated to be provided to patients for two years; one clinician expressed uncertainty about whether olaparib would be used until disease recurrence. High grade serous ovarian cancer patients were identified as a subgroup of interest for use of olaparib. As stated by one clinician, they would use olaparib exactly as it was represented in the trial; first they would identify a patient's germline/somatic cell results, evaluate for complete or partial response and offer olaparib immediately upfront to maintain this outcome.

Clinical relapse was stated to be an inevitable occurrence, as patients are watched every three months. Using poly(ADP-ribose) polymerases inhibitors (PARPi) upfront can delay the progression patients will eventually face, and provide patients with a safe and efficacious treatment. This clinician expressed having used olaparib on select patients with private insurance coverage after a second relapse and found that the treatment was tolerable. One joint clinician input commented on the safety profile of olaparib, stating that it is consistent with that seen in patients with relapsed disease. Other benefits of olaparib among high risk patients were stated to be the ease of use, the superior safety profile, and tolerability compared to bevacizumab.

5.4 Sequencing and Priority of Treatments with Olaparib

One of the joint clinician inputs from CCO suggested that olaparib would follow normal sequencing options in Ontario, and that olaparib maintenance would replace observation for most BRCA mutated patients. Olaparib would be a new treatment option in this setting. The other joint clinician input indicated the current sequence is carboplatin with taxol for six cycles with upfront or interval surgery, followed by olaparib for patients with a complete or partial response (at least 30% reduction in disease) to first line treatment. All clinicians agreed that olaparib would be used upon completion of first line therapy in patients with a clinical response.

Two clinicians commented on bevacizumab for patients with ovarian cancer; one clinician stated that bevacizumab is not routinely used in this setting, therefore no therapy would be replaced with the approval of olaparib. The other clinician expressed dissatisfaction with bevacizumab and found the study results to be conflicting and the tolerability of bevacizumab to be modest. This clinician stated that they typically sequence patients with platinum doublet chemotherapy after debulking procedures and then watch and wait for relapse. After, patients are classified as platinum sensitive or not, and following therapies are chosen accordingly. Bevacizumab was stated to be used in the palliative setting of platinum resistance. Therefore, the initiation of upfront PARPi would not change the sequence.

5.5 Companion Diagnostic Testing

All clinicians identified that patients will to be tested for BRCA status, and germline and/or somatic BRCA testing was available at their centres. Two clinicians acknowledged that upfront germline testing has been embraced over the past seven years and has led to greater knowledge of patient mutations; all patients with high grade serous ovarian cancer currently receive BRCA germline testing. One clinician input identified BRCA germline testing is available at their centre, and two clinician inputs identified BRCA testing was available but did not specify if it was germline and/or somatic testing that was available. Two clinician inputs indicated both somatic (tumor testing on a biopsy or surgical specimen) and germline testing should be done and is available at their centres. Specifically, one clinician mentioned that physician-initiated testing in the germline setting was evaluated in their centre and was found to be quicker to initiate and complete the process of patient identification. The other joint clinician input indicated that testing for BRCA status occur for all high-grade epithelial ovarian cancer patients, including patients with high-grade endometrioid histological subtypes. Expedited germline testing was suggested to ensure timely results of BRCA germline status for patients with low cellularity or who do not have enough tumour sample to conduct somatic BRCA testing. In addition to BRCA testing, the joint clinician input suggested all patients to be referred to genetics for assessment.

5.6 Implementation Questions

5.6.1 In regards to question 3.2 above, the eligibility criteria for the SOLO-1 trial included a specific patient population compared to the broader funding request. In clinical practice, is there evidence to extend the use of olaparib to (provided all other eligibility criteria are met):

5.6.1.1 Patients who received bevacizumab during their first-line course of treatment, either in combination or as maintenance therapy following combination therapy

None of the clinicians agreed that olaparib should be extended to patients who received bevacizumab as first-line treatment, as there is currently no evidence to suggest efficacy. One clinician highlighted the lack of evidence for use of olaparib for patients who received bevacizumab. One clinician identified a trial that showed improvement in PFS with olaparib in combination with cediranib, however it was limited to non-BRCA mutated patients. No trials were identified specific to combination olaparib and bevacizumab. One of the joint inputs stated that olaparib should not be given concurrently with another therapy. BRCA mutated patients who began maintenance bevacizumab prior to funding of maintenance olaparib were recommended by the joint clinician input to be grandfathered and allowed the option of switching to olaparib if it is determined to be the preferred therapy. The group of

joint clinicians also made note that bevacizumab is currently funded for eligible patients with platinum-resistant disease, such that eligible patients can receive bevacizumab later if their disease recur.

5.6.1.2 Patients with early stage disease (FIGO Stage I, IIA, IIB, or IIC)

Clinicians from one joint input were unsupportive of providing olaparib to patients with stage I disease. However, this group of clinicians were supportive of using olaparib on patients with stage II disease as many of these patients have inadequate surgery or have occult disease unidentified by surgery. Stage II patients would likely benefit from olaparib maintenance therapy due to the peritoneal involvement that many stage II patients face putting them at high risk for recurrence. One of the single clinician inputs also agreed that patients with stage II disease would benefit from olaparib, since the pathophysiology of stage II and III was noted to be the same. On the other hand, another single clinician input indicated there was no evidence to extend the use of olaparib to early stage disease. The other group of clinicians was, however, unsupportive of extending use of olaparib to patients with stage I, IIA, IIB, or IIC patients.

5.6.1.3 Patients who have previously received chemotherapy (i.e., adjuvant) for prior diagnosis at an earlier stage for their ovarian, fallopian tube or primary peritoneal cancer

One of the joint clinician inputs suggested extending the use of olaparib to patients who experienced recurrence after having previously received chemotherapy, but not to patients in the third line. Similarly, another clinician indicated that patients treated previously in the adjuvant setting may still qualify under the umbrella of second relapse, but only if they remain platinum sensitive. The second joint clinician input and another single clinician also agreed that extending to this population was acceptable; the patients referred to as part of 5.6.1.3 were considered to be similar to patients part of the SOLO2 trial, and that there was evidence to recommend the use of olaparib among these patients so long as they had not received olaparib previously.

5.6.1.4 Patients who are not surgical candidates, in the trial stage III patients must have had one attempt at optimal debulking surgery (upfront or interval debulking) and stage IV patients must have had either a biopsy and/or upfront or interval debulking surgery

Both joint inputs agreed that olaparib may be used for patients who are not surgical candidates, so long as patients had at least one response to chemo, according to one of the joint inputs; the second joint input stated that stage III patients, including those who have any tissue diagnosis of high grade epithelial ovarian, fallopian tube, primary peritoneal and high-grade endometrioid cancer, who are not surgical candidates should be eligible for olaparib based on their biopsy results and so long as they satisfy other eligibility criteria. However, two of the single clinician inputs disagreed, stating that there is no data to suggest use of olaparib among this specific patient population.

5.6.1.5 There is a small number of patients who may be allergic to or unable to tolerate platinum-based chemotherapy, and therefore would have non-platinum therapy.

For patients who may be allergic or cannot tolerate platinum-based chemotherapy, use of olaparib was supported by some clinicians but not by others. One of the joint clinician inputs recommended using olaparib after they received treatment with non-platinum-based chemotherapy. The other joint input stated that, while such patients

were not studied, if they were BRCA positive they should be considered for olaparib. A single clinician also identified that there was no data regarding use of olaparib for this population of patients. Platinum sensitivity was identified to be extremely rare, however hypersensitivity protocols allow for patients to be treated successfully allowing for platinum response to be evaluated. For patients who are unable to receive platinum-based chemotherapy, the clinician suggested evaluating patients on a case by case basis, as there is no evidence to suggest use of olaparib, but the patients may still benefit especially if they have renal disease.

One clinician stated that use of olaparib should be limited to women with some form of HRD.

5.6.2 In regards to question 3.4 above, please consider the optimal sequencing of treatment for patients following olaparib monotherapy maintenance in this setting:

5.6.3 What treatment options would be available to patients upon progression of olaparib?

5.6.4 Is it appropriate to use olaparib as second-line treatment for platinum-sensitive disease, as per the previous pERC recommendation for olaparib (as monotherapy maintenance treatment of adult patients with platinum-sensitive relapsed BRCA-mutated epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response to platinum-based chemotherapy)?

For patients who progress on olaparib, clinicians from multiple inputs suggested the use of chemotherapy, and, in some cases, surgery depending on the nature and location of the tumours. Patients may be candidates for platinum-based regimens, paclitaxel alone, or other therapy if toxicity is a concern. Patients may also be eligible for clinical trials.

Two joint inputs and one single clinician input agreed that olaparib may be used in the second-line as long as patients had not previously received olaparib and that it be used in the recurrent setting. However, it was acknowledged that olaparib is much more effective if given in the first-line setting. Two inputs stated that olaparib would optimally be used in the first line and that waiting until the disease has progressed or recurred would not help to improve survival. In addition, one joint input and one individual clinician input indicated that no evidence exists to support repeat treatment or rechallenging with another PARPi in the setting of further platinum therapy; olaparib was suggested to be restricted to one line. The joint input acknowledged that there may be in the future data on re-challenging patients with PARPis as the space is evolving.

5.6.3 In clinical practice, if olaparib was available:

5.6.3.1 How frequently should disease be assessed while on olaparib?

5.6.3.2 What are the stopping rules for olaparib (e.g., rising CA-125 levels or combination of rising CA-125 levels and radiological progression)?

5.6.3.3 Whether olaparib could be considered for patients who have completed platinum based chemotherapy more than eight weeks ago and what

maximum time between completion of chemotherapy and commencement of olaparib would be appropriate?

Both joint clinician inputs stated that disease should be as assessed as per current clinical practice. One joint input stated specifically that disease should be assessed by a combination of clinical symptoms, CA-125 levels, and imaging when alterations are noted in one of the above. Two of the individual clinician inputs agreed that disease should be assessed monthly while on treatment with labs and on a clinical basis. Another clinician stated that disease should be reassessed every three months.

Stopping rules were suggested to be based on radiological progression by one joint clinician input. Another joint input suggested using a combination of criteria as sometimes rising CA-125 levels, if not significantly rising, can be unspecific to disease progression. Two other individual clinicians agreed that radiologic evidence of disease progression or clinical evidence of progression would be used as a stopping rule, not rising CA-125 levels. Radiologic assessment was recommended to take place as per the pivotal trial or slightly longer if patients do not show any symptoms of progression. Intolerance to olaparib was also suggested as another stopping rule.

Finally, both joint clinician inputs and one individual input agreed that patients should begin treatment with olaparib within 8 weeks of completing platinum-based chemotherapy. However, one clinician stated that allowances may be required for some cancer centres that do not have streamlined processes for BRCA testing, suggesting an extended window of nine to twelve weeks in the absence of clinical changes and stability of CA-125 levels and radiological disease. One of the joint inputs also identified that under extenuating circumstances, some patients should be considered on a case by case basis if they have no evidence of disease progression, provide an explanation for why treatment could not commence within eight weeks, and meet all other aspects of the inclusion criteria.

5.6.4 In the SOLO-1 trial, eligible patients had a deleterious or suspected deleterious germline or somatic BRCA1/2 mutation. In clinical practice, what definitions of deleterious BRCA mutation are used?

One joint input and two individual inputs from clinicians agreed the same definitions used in the SOLO-1 trial are used in clinical practice. Another joint input stated that patients with pathogenic or likely pathogenic mutations are also considered as part of the definition of deleterious BRCA mutations. Another clinician stated that variant mutations of unknown significance would need to be excluded from definitions of deleterious BRCA mutations, and that confirmation of deleterious mutations should be made by a genetic counsellor.

5.6.5 In clinical practice, can BRCA testing be somatic or germline? Is there a preference for somatic or germline?

Both somatic and germline testing were stated to be used in clinical practice by all inputs. One joint input stated that germline testing is easier and widely available but may not be as efficacious as somatic testing. Another joint input suggested that somatic reflex testing be conducted at the time of initial diagnosis and made widely available in all jurisdictions. One of the individual clinician inputs stated that, while evidence supports both somatic and germline testing, somatic testing should be considered first followed by germline testing. However, another individual clinician

input expressed preference for germline testing over somatic testing. The clinician stated that in their centre a physician-initiated process has allowed for straightforward cases, such as high-grade serous patients, to begin initiation of germline testing at a patient's first consultation. Germline testing was also stated to have a quicker turnaround time than somatic testing, for example, when patients have interval debulking.

6 SYSTEMATIC REVIEW

6.1 Objectives

The primary objective of this review is to evaluate the efficacy and safety of olaparib (Lynparza) monotherapy for the maintenance treatment of adult patients with newly diagnosed, advanced, BRCA-mutated, high-grade, epithelial ovarian, fallopian tube, or primary peritoneal cancer, who are in response (complete or partial) to first-line platinum-based chemotherapy.

Supplemental Questions and Comparison with Other Literature most relevant to the pCODR review and to the Provincial Advisory Group were identified while developing the review protocol and are outlined in section 7 and section 8.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold. The literature search strategy and detailed methodology used by the pCODR Methods Team are provided in Appendix A.

Table 6.1: Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
<p>Published or unpublished RCTs</p> <p>In the absence of RCT data, fully published clinical trials investigating the safety and efficacy of olaparib should be included.</p>	<p>Adult patients (≥ 18 years of age) with newly diagnosed, advanced, BRCA-mutated high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer, who are in response (complete or partial response) to first-line platinum-based chemotherapy</p> <p><u>Subgroups:</u></p> <ul style="list-style-type: none"> - Age - ECOG PS - Tumor type (epithelial ovarian vs. fallopian tube vs. peritoneal) - BRCA 1 vs. 2 mutation - Response type (complete vs. partial) - Stage (III vs. IV) - Number of cycles of platinum (4-6 vs. 7+) 	<p>Olaparib (Lynparza) monotherapy</p>	<p>Placebo</p> <p>Bevacizumab</p>	<p><u>Primary:</u></p> <ul style="list-style-type: none"> - PFS - OS <p><u>Secondary:</u></p> <ul style="list-style-type: none"> - ORR - TTP - DOR - HRQoL <p><u>Exploratory:</u></p> <ul style="list-style-type: none"> - Time to start next chemo <p><u>Safety:</u></p> <ul style="list-style-type: none"> - AEs - TRAEs - SAEs - WDAEs
<p>Abbreviations: AE = adverse event; BRCA = breast cancer gene; DOR = duration of response; ECOG PS = Eastern Cooperative Oncology Group Performance Status; HRQoL = health-related quality of life; ORR = objective response rate; OS = overall survival; PD-L1 =</p>				

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
programmed death-ligand 1; PFS = progression-free survival; RCT = Randomized controlled trial; SAE = serious adverse event; TRAEs = treatment-emergent adverse events; TTP = time to progression; WDAEs = withdrawals due to adverse events				

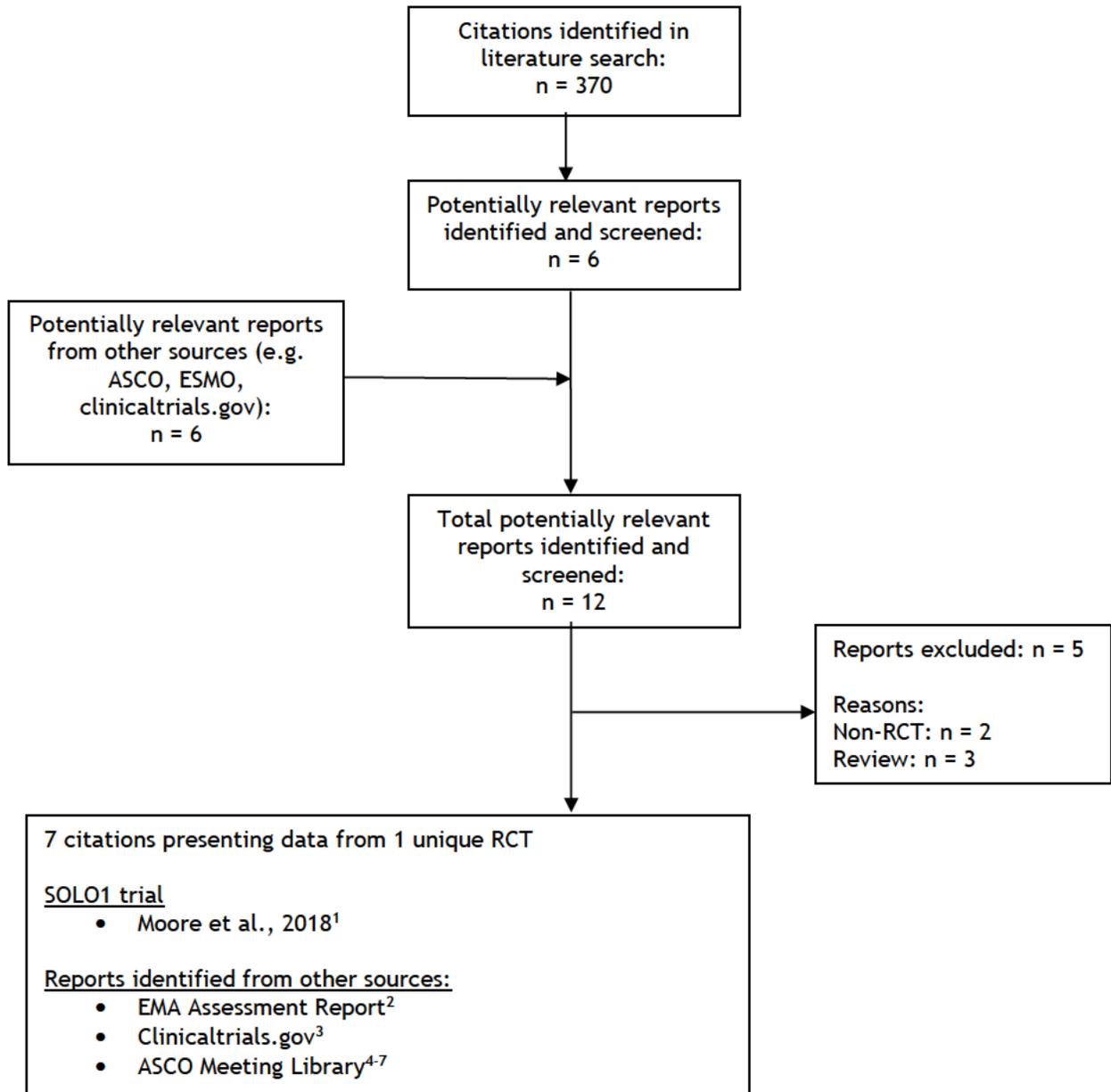
* Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)

6.3 Results

6.3.1 Literature Search Results

Of the 12 potentially relevant reports identified, 7 citations were included in the pCODR systematic review¹⁻⁷ and 5 citations were excluded³⁸⁻⁴². Citations were excluded because the study design was either a non-randomized clinical trial or a review.

Figure 1. QUOROM Flow Diagram for Inclusion and Exclusion of studies



Note: Additional data related to the SOLO1 trial were also obtained through requests to the Submitter by pCODR.^{8,9,43-45}

6.3.2 Summary of Included Studies

One randomized controlled clinical trial (RCT), SOLO1, met the selection criteria for this systematic review.¹ Key trial characteristics including study design, eligibility criteria, intervention details, and trial outcomes, are summarized in Table 6.2.

6.3.2.1 Detailed Trial Characteristics

Table 6.2: Summary of Trial Characteristics of the SOLO1 trial

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
<p>Study:^{1,9} SOLO1 NCT01844986</p> <p>Characteristics: Double-blind, randomised (2:1), placebo-controlled, superiority, phase III trial</p> <p>N=391 randomized (olaparib=260; placebo=131)</p> <p>N=390 treated (olaparib=260; placebo=130)</p> <p>Setting: 118 sites in 15 countries including Canada, Australia, Brazil, China, France, Israel, Italy, Japan, Netherlands, Poland, Russia, South Korea, Spain, United Kingdom, and United States</p> <p>Patient Enrolment Dates: September 3rd, 2013 to March 6th, 2015</p> <p>Data cut-off: May 17th, 2018</p> <p>Final Analysis Date: To be conducted when OS data reach ~60% maturity</p> <p>Funding: AstraZeneca and Merck</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • ≥18 years of age • FIGO stage III to IV BRCA mutated high grade serous or high grade endometrioid ovarian cancer, primary peritoneal cancer, and/or fallopian tube cancer who have completed first-line, platinum based chemotherapy (intravenous or intraperitoneal) • CR to platinum therapy with no evidence of measurable disease based on post-treatment scan and normal CA-125 level, or PR defined as ≥30% reduction in tumor volume from start to finish of chemotherapy or no evidence of measureable disease on post-treatment scan with CA-125 that has not decreased to normal range • FIGO stage III patients must have had one attempt at optimal debulking surgery and stage IV patients must have had a biopsy and/or one interval debulking surgery • BRCA1 or BRCA2 mutation predicted or known to be deleterious • Patients must have completed first line platinum-based regimen (carboplatin or cisplatin administered through IV or IP) consisting of a min. of 6 cycles and a max. of 9 (unless discontinued due to toxicity then 4 cycles min.) • No prior bevacizumab • Last dose of chemotherapy was ≤ 8 weeks prior to randomisation • CA-125 level ≤ ULN • Adequate organ and bone marrow function • ECOG PS 0-1 <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> • BRCA1/2 mutations that are non-detrimental • SD or PD following first line chemotherapy • More than one debulking surgery prior to randomisation • Previous diagnosis and treatment of abdominal or pelvic tumors including earlier stage ovarian, fallopian tube, or primary peritoneal cancer 	<p>Intervention: Olaparib 300 mg BID</p> <p>Comparator: Placebo BID</p>	<p>Primary:</p> <ul style="list-style-type: none"> • PFS <p>Secondary:</p> <ul style="list-style-type: none"> • Time from randomisation to second progression (PFS2) • OS • TFST • TSST • TDT • TTP • ORR • HRQoL <p>Exploratory:</p> <ul style="list-style-type: none"> • Exploratory HRQoL analyses <p>Safety</p>

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
	<ul style="list-style-type: none"> • Past history of endometrial cancer or other malignancy within last 5 years • Previous treatment with a PARPi or investigational agent • Concomitant use of known potent CYP3A4 inhibitors • Patients with MDS or AML • Symptomatic uncontrolled brain metastases • Immunocompromised patients (e.g. HIV-positive) • Active HBV or HCV • Previous allogenic bone marrow transplant • Blood transfusion \leq120 days prior to study entry • Drainage of ascites during final 2 cycles of chemotherapy prior to study entry 		
Abbreviations: AML = acute myeloid leukemia; BID = twice daily; BRCA = breast cancer gene; CA-125 = cancer antigen 125; CR = complete response; CYP3A4 = cytochrome P450 3A4; ECOG PS = Eastern Cooperative Oncology Group Performance Status; FIGO = International Federation of Gynecology and Obstetrics; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HRQoL = health-related quality of life; IP = intraperitoneal; IV = intravenous; max. = maximum; MDS = myelodysplastic syndromes; mg = milligram; min. = minimum; ORR = objective response rate; OS = overall survival; PARPi = poly (ADP-ribose) polymerase inhibitor; PD = progressive disease; PFS = progression-free survival; PR = partial response; TDT = time from randomisation to study treatment discontinuation or death; TFST = time from randomisation to first subsequent therapy; TSST = time from randomisation to second subsequent therapy or death; TTP = time to progression; SD = stable disease; ULN = upper limit of normal			

Table 6.3: Select quality characteristics of included studies of olaparib in patients with ovarian, peritoneal, and/or fallopian tube cancer

Study	Treatment vs. Comparator	Primary outcome	Required sample size	Sample size	Randomization method	Allocation concealment	Blinding	ITT Analysis	Final analysis	Early termination	Ethics Approval
SOLO1 ¹	Olaparib vs. Placebo	PFS	344	391	2:1, via a blocked randomisation scheme IVRS/ IWRS	Yes, using a unique Kit ID number linked to the randomisation scheme	Yes	Yes	Yes	No	Yes
Abbreviations: ID = identification; IVRS = interactive voice response system; IWRS = interactive web response system; PFS = progression-free survival											

a) Trials

SOLO1 was an international, double-blind, phase 3, superiority, RCT of olaparib versus placebo in the maintenance setting for patients with newly diagnosed advanced ovarian, fallopian tube, and/or peritoneal cancer with a germline or somatic mutation in BRCA1, BRCA2, or both, who had a complete response (CR) or partial response (PR) after first-line platinum-based chemotherapy.¹ This study was

conducted at 118 sites in 15 countries, which are listed in Table 6.2, and included 82 Canadian patients from 7 participating sites in Ontario (4 sites) and Quebec (3 sites).⁹

Trial Design

A summary of the SOLO1 study design can be found in Figure 6.2.

Screening and Randomisation

Patients were assessed for eligibility during the screening visit of the study, and key inclusion and exclusion criteria are outlined in Table 6.2. Briefly, eligible patients had newly diagnosed, histologically confirmed, advanced International Federation of Gynaecology and Obstetrics (FIGO) Stage III or IV BRCA mutated high grade serous or high grade endometrioid (based on local histopathological findings) ovarian cancer, primary peritoneal cancer, and/or fallopian tube cancer who were in investigator-assessed complete response (CR) or partial response (PR) following the completion of first-line platinum-based chemotherapy. Clinical CR was defined as no evidence of measurable or non-measurable disease assessed using response evaluation criteria in solid tumors (RECIST) at the post-chemotherapy scan and normal cancer antigen 125 (CA-125) levels. PR was defined as $\geq 30\%$ reduction in RECIST measurable or non-measurable disease from the start to completion of first-line platinum chemotherapy, or no radiological evidence of disease at the end of chemotherapy with CA-125 level above the normal range. Stage III patients must have had only one attempt at optimal debulking surgery, and stage IV patients must have had a biopsy and/or upfront or interval debulking surgery.¹

With regards to the first-line platinum-based therapy received, patients must have completed a minimum of 6 cycles and a maximum of 9 cycles of treatment, except for patients who discontinued due to toxicity related to the platinum regimen (in this case, a minimum of 4 cycles of treatment was acceptable). Patients must not have received bevacizumab (either in combination with platinum-based therapy or as maintenance therapy) or other investigational agents with first-line therapy.¹

Patients must have had a deleterious or suspected deleterious germline or somatic BRCA mutation to be eligible based on blood or tumor local testing. Potentially eligible patients with unknown BRCA mutation status could consent to central BRCA mutation testing to determine eligibility. All patients were required to provide a blood sample for confirmatory germline BRCA mutation by the Myriad test, or for those in China, the BRCA 1/2 genetic testing assay (BGI). Patients were also required to provide an archival tumor sample for central testing. Patients were randomised within 8 weeks after their last dose of chemotherapy using an Interactive Voice Response System (IVRS)/Interactive Web Response System (IWRS) in a 2:1 ratio to olaparib at a dose of 300 mg, twice a day, or to matching placebo. Randomisation was stratified by investigator-assessed response (complete response [CR] vs. partial response [PR]) to first line platinum therapy.¹

Treatment

Patients had weekly clinic visits for the first 4 visits following randomisation and then every 4 weeks thereafter. Patients continued study treatment for up to 2 years or until investigator-assessed radiographical progressive disease (PD) per RECIST (irrespective of rises in CA-125), whichever occurred first, and if in the investigator's opinion they were benefitting from treatment and did not meet other discontinuation criteria. Patients could be discontinued from study treatment due to adverse events (AEs), patient decision, severe non-compliance to the study

protocol, bone marrow findings consistent with myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML), PD according to RECIST criteria (unless in the investigator's opinion they were benefitting from treatment and did not meet any other discontinuation criteria listed in this section), or if at 2 years the patient had no evidence of disease (NED). Patients with stable disease (SD) at 2 years, or those with PD, could continue to receive study treatment if determined to be in the patient's best interests by the investigator. Continuing treatment beyond 2 years was made on a case-by-case basis in consultation with the AstraZeneca study physician and after assessment of the patient's disease status based on modified RECIST guidelines and assessment of the patient's clinical condition.¹

Follow-Up

Following discontinuation or PD, patients were seen 30 days post-discontinuation for study evaluations that included vital signs, electrocardiogram (ECG), hematology/clinical chemistry, and quality of life assessments. Participants were followed up every 12 weeks for second progression-free survival (PFS2) and survival, and further treatment was at the discretion of the investigator. Participants were additionally contacted 7 days prior to the data cut-off date for the survival analysis. Crossover to olaparib was not permitted in the trial, however patients could receive olaparib outside the trial. Information on further systemic anti-cancer therapy was collected until death, loss to follow-up, or withdrawal of consent. Overall survival data was collected for patients who were lost to follow-up or withdrew consent from hospital records or public death registries, where available.¹

Disease Assessments

Participants had disease assessments assessed according to RECIST at baseline, every 12 weeks for up to 3 years, followed by every 24 weeks until radiological PD according to modified RECIST. RECIST was modified to assess patients with clinical CR at study entry who were assessed as having NED. Disease assessments were conducted using computed tomography (CT) or magnetic resonance imaging (MRI) scans. All scans were sent to a Clinical Research Organization (CRO) for blinded independent central review (BICR). Following progression-free survival (PFS) analysis, central review of scans was not required, and thus, all ongoing assessments are by local site assessment only.¹

Sample Size

Sample size was determined based on the primary endpoint of PFS. To detect an assumed true treatment effect of a hazard ratio (HR) of 0.62 with 206 PFS events and a two-sided significance level, the study has 90% power at $\alpha=0.05$. This translates into an eight month benefit in median PFS over 13 months on placebo, as estimated from data reported by Alsop et al., 2012, if PFS is exponentially distributed. Approximately, 344 patients were planned for recruitment (2:1 ratio), so that data maturity (follow-up time) for the PFS analysis was ~60%. The original assumptions for the study design were described to have been overestimated as the rate of PFS events was lower than projected, and the protocol was amended to analyze PFS when 196 events occurred (~50% maturity), or 3 years after the last patient had been randomised,, whichever came first.¹

Study Endpoints and Statistical Analyses

Primary Endpoint - Progression-free survival (PFS)

The primary endpoint was PFS, defined as the time from randomisation until the date of investigator-assessed PD according to RECIST or death (by any cause), regardless of treatment discontinuation or the use of another anticancer therapy prior to PD. Patients were censored at the latest evaluable visit if they had not progressed or died at the time of the analysis, or had progressed or died after two or more missed visits. If the patient did not have a baseline assessment, they were censored at Day 1 unless they died within 2 visits of baseline. PFS time was derived based on scan/assessment dates, not visit dates.¹

PFS was evaluated by comparing olaparib to placebo using a log-rank test stratified by response to first-line platinum chemotherapy (i.e., CR or PR as assessed by the investigator) to generate the p-value and using the Breslow approach for handling ties. Cox proportional hazards (PH) model was used to estimate the hazard ratio (HR) and confidence interval (CI), with the stratification variable (i.e. response) as a covariate and Efron's approach for handling ties. CIs were calculated using a likelihood approach. The Kaplan-Meier (K-M) methodology was used to estimate event rates over time within each treatment arm and presented in a plot.¹

Subgroup Analyses

Subgroup analyses were conducted to assess the consistency of treatment effect across potential or expected prognostic factors, unless too few events (<20 events per subgroup level) did not permit a meaningful analysis. For each subgroup the HRs and associated CIs were calculated using the Cox PH model with Efron's tie handling that contained the treatment term, subgroup, and treatment by factor interaction term. The pre-specified subgroups included:

- Response to previous platinum chemotherapy (CR or PR)
- Germline BRCA mutation, wildtype, or variant of uncertain significance or missing as assessed by Myriad test
- Tumor BRCA mutation status confirmed by Foundation Medicine testing
- Eastern Cooperative Oncology Group performance status (ECOG PS) at baseline (0 or 1)
- Baseline CA-125 value (\leq ULN or $>$ ULN)
- BRCA mutation (BRCA1 or BRCA2 or both)
- Age at randomisation ($<$ 65 or \geq 65)
- Stage of disease at initial diagnosis (FIGO Stage III or IV)
- Residual macroscopic disease following debulking surgery prior to entry into the study or no residual macroscopic disease
- Regional (North America vs. Rest of World; Brazil, Poland, Russia, Japan, Korea vs. Rest of World)
- Race (White or Black/African-American or Asian or Native Hawaiian/Pacific Islander or American Indian/Alaska Native or Others)¹

Sensitivity Analyses

A number of sensitivity analyses for PFS were conducted using the same methodology for the primary analysis of PFS. The following sensitivity analyses were conducted:

- BRCA mutation: PFS was analyzed excluding patients who did not have a germline BRCA mutation confirmed by the central Myriad test, as well as an additional analysis excluding any patients that did not have a tumor BRCA mutation confirmed by Foundation Medicine.
- Evaluation time bias: RECIST assessments and scan contributing to a specific visit could be performed on different dates outside the protocol-scheduled time points that could have introduced evaluation-time bias. The midpoint between the time of progression and previous evaluable RECIST assessment was analysed using the investigator assessments.
- Attrition bias: The PFS analysis was repeated by using the actual PFS times for patients who were censored due to 2 or more missing/non-evaluable tumor assessments. In addition, patients who took subsequent therapy prior to PD or death were censored at the last evaluable assessment prior to taking the subsequent therapy.
- Ascertainment bias (also referred to as the BICR assessment): The PFS analysis was repeated using BICR-assessments of RECIST disease. Important discrepancies between investigator and BICR assessments were summarized.
- Deviation bias: If meaningful to perform, a sensitivity analysis excluding patients with deviations that could affect the efficacy of the study treatment was planned. This included if >10% of patients did not have the intended disease or indication or did not have any randomised treatments.¹eCRF stratification variable: The PFS analysis was repeated using the eCRF stratification variables, as discrepancies between eCRF and IVRS are known to occur.²
- Possible informative censoring: Informative censoring may have occurred with patients who progressed according to the investigator, but not according to BICR. A sensitivity analysis was conducted based on BICR where informatively censored patients were assumed to have an event 12-weeks after the investigator-assessed event that was in discordance with the BICR assessment.^{2,9}
- Earliest investigator/BICR assessment of PD: A sensitivity analysis of PFS was performed using the earliest of investigator or BICR assessment of PD.
- Additional sensitivity analysis: The HR and CI, and stratified log-rank test, for PFS were estimated using U and V statistics to assess the robustness of the primary analysis methodology.²
- Progression-free at 24 months (PFS24): The stratified K-M estimate of PFS at 24 months was estimated by treatment group. The difference in the stratified estimates of PFS24 were calculated and the 95% CIs were estimated using Greenwood's estimate of variance of the K-M proportion.^{1,2}

Multiplicity

A multiple testing procedure was employed to control the Type I error at 2.5% (1-sided) across the primary endpoint of PFS and key secondary endpoints of PFS2 and overall survival (OS).¹

Secondary Endpoints

Secondary endpoints included:

- Time from randomisation to second progression (PFS2): PFS2 was defined as the time from randomisation to the earliest PD or death event subsequent to the one used for the primary analysis of PFS. The date of second progression was recorded by the investigator and defined according to local standard clinical practice and could involve investigator-assessed radiological PD, CA-125 elevation above the normal range, symptomatic progression, or death. Patients were censored at the last time known to be alive and without a second PD if they were alive at data cut-off and did not have a second PD. If the patients experienced a second PD after 2 or more missed visits, the patient was censored at the time of the latest evaluable investigator-recorded assessment.
 - The initial PFS2 analysis was performed at the same time as the PFS analysis and used the same methodology. A further PFS2 analysis is planned when the data are 60% mature, unless PFS2 was found to be statistically significant at the time of initial analysis.
 - Sensitivity analyses included:
 - PFS2 analysis repeated using BICR data in those with germline BRCA mutation confirmed by Myriad testing and those with tumor BRCA mutation confirmed by Foundation Medicine.
 - K-M plot of the time to censoring where the censoring indicator of the primary PFS2 was reversed.
 - Marginal model approach to be performed where patient risks were partitioned from randomisation to PFS and from PFS to PFS2.¹
 - Exploratory analyses included:
 - PFS2 adjusted by subsequent PARPi if sufficient proportion of patients switched, and choice of methods would be based on the blinded review of the data and plausibility of underlying assumptions.⁸
- Overall survival (OS): This was defined as the time from the date of randomisation until death due to any cause. Any patient not known to have died at the time of analysis was censored at the last recorded date the patient was known to be alive. The same methodology for analysis as PFS was used for the analysis of OS, provided there were sufficient number of events for analysis (≥ 20 deaths). Further analyses of OS are planned to be performed when the data is 60% mature.
 - Sensitivity analyses included:

- OS analysis repeated those with germline BRCA mutation confirmed by Myriad testing and those with tumor BRCA mutation confirmed by Foundation Medicine.
 - K-M plot of the time to censoring where the censoring indicator of the primary OS was reversed.
 - Subgroup analyses with the same methodology and subgroups identified for the PFS analysis.
 - Exploratory analyses included:
 - OS adjusted by subsequent PARPi if sufficient proportion of patients switched, and choice of methods would be based on the blinded review of the data and plausibility of underlying assumptions.
- Time from randomisation to start of first subsequent therapy or death (TFST): Subsequent therapies were reviewed to assess which were clinically important treatments intended to control ovarian cancer. Patients who were not known to have died and not known to have a first post study treatment were censored at the last known time to not have received a subsequent therapy (i.e., the last follow-up visit where this was confirmed). The same methodology for the analysis of PFS was used for the analysis of TFST, however, no multiple adjustment will be applied as these are viewed as supportive endpoints. A sensitivity analysis was conducted in patients with germline BRCA mutation confirmed by Myriad testing and those with tumor BRCA mutation confirmed by Foundation Medicine.
- Time from randomisation to start of second subsequent therapy or death (TSST): Patients who were not known to have died and not known to have a second post study treatment were censored at the last known time to not have received a subsequent therapy (i.e., the last follow-up visit where this was confirmed). The same methodology for the analysis of PFS was used for the analysis of TSST, however, no multiple adjustment will be applied as these are viewed as supportive endpoints. A sensitivity analysis was conducted in patients with germline BRCA mutation confirmed by Myriad testing and those with tumor BRCA mutation confirmed by Foundation Medicine.
- Time to study discontinuation or death (TDT): This was defined as the time from the date of randomisation to the date of study treatment discontinuation or death. Any patient not known to have died at the time of analysis and not known to have discontinued study treatment was censored at the last recorded time the patient was known to be alive. The same methodology for the analysis of PFS was used for the analysis of TDT; however, no multiple adjustment will be applied as these are viewed as supportive endpoints. A sensitivity analysis was conducted in patients with germline BRCA mutation confirmed by Myriad testing and those with tumor BRCA mutation confirmed by Foundation Medicine.
- Time to earliest progression by RECIST 1.1, CA-125, or death: Defined as the time from randomisation to the earlier date of time to progression by RECIST, progression or recurrence based on progressive serial elevation of serum CA-125 according to the modified Gynaecological Cancer Intergroup (GCIG) criteria, or death. Patients without CA-125 progression or a RECIST

progression who were alive at the time of analysis were censored at the last evaluable RECIST assessment or last available CA-125 measurement, whichever was more recent. The same methodology as used for the analysis of PFS was used for the time to progression by RECIST 1.1 or CA-125; however, no multiple adjustment will be applied as these are viewed as supportive endpoints.

- Best overall RECIST response (BoR): BoR was defined as the best response a patient had during their time in the study following randomisation, but prior to starting any subsequent cancer therapy and prior to RECIST progression or the last evaluable assessment in the absence of RECIST progression. BOR was determined by the investigator using RECIST criteria and categories included CR, PR, SD, NED (only applicable to patients entering the study with no disease at baseline), PD, and not evaluable (NE).
- Health-related quality of life (HRQoL), which was assessed using the Trial Outcome Index (TOI) score on the Functional Assessment of Cancer Therapy-Ovarian Cancer (FACT-O) questionnaire. FACT-O is composed of physical, social/family, emotional, and functional well-being sub-scales, in addition to an additional scale specific to ovarian cancer symptoms. The TOI score is the sum of scores from 25 items included in the physical well-being (7 items), functional well-being (7 items), and ovarian cancer sub-scales (11 items), and scores range from 0 to 100 with higher scores indicating better HRQoL. A difference of 10 points is considered clinically relevant, or a minimally important difference. The FACT-O score is the sum of all the individual sub-scale scores, and ranges from 0 to 152, with a higher score indicating higher HRQoL. The primary HRQoL analysis was evaluated using a mixed model for repeated measures (MMRM) analysis of change from baseline in TOI scores for each visit. The MMRM included patient, treatment, visit, and treatment by visit interaction as explanatory variables, the baseline TOI score as a covariate along with the baseline TOI score by visit interaction. Adjusted mean estimates per treatment group and corresponding 95% CIs, as well as an estimate of the treatment difference, 95% CI, and p-value were presented.
 - A time-adjusted area under the curve (AUC) analysis was also performed for TOI using the first 24 months of data provided by a patient. The estimated mean difference between treatment groups, 95% CI, and p-value were also presented. Patients who died during the first 24 months had their data set to 0 for each question in the FACT-O from time of death until 24 months. In addition, an analysis using all available data for each patient was performed.¹

Exploratory outcomes

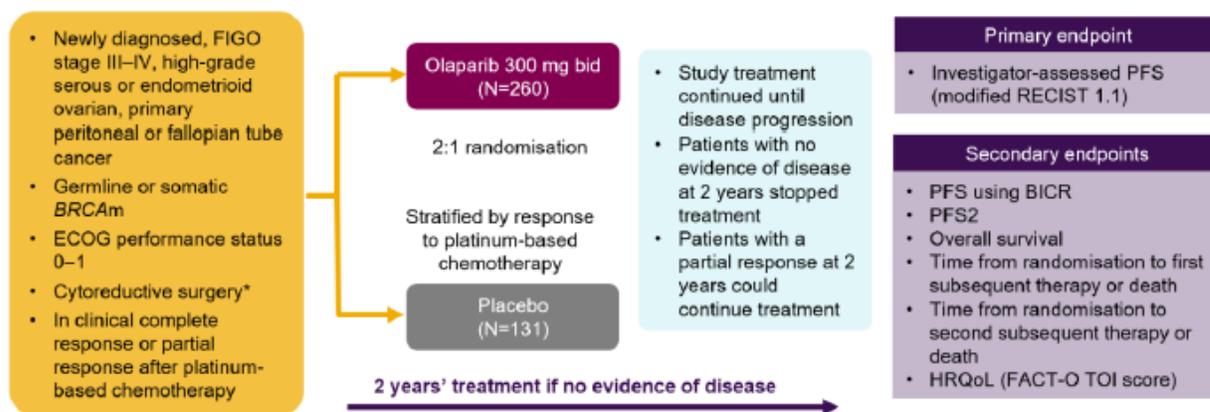
- The EuroQoL five dimensions (EQ-5D-5L) questionnaire comprises of 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and is a standardised measure of health status that provides a generic measure of health. Dimensions are rated on a 5-point scale of increasing levels of severity (no problems, slight problems, moderate problems, severe problems, and unable to/extreme problems). A unique health state is referred to by a 5-digit code, which was converted into a weighted health state index. The EQ-5D-5L also includes a visual analogue scale (VAS), in which the participant rates their general state of health from 0 (worst imaginable health) to 100 (best imaginable

health). Health state utility values and VAS were summarised descriptively by visit, as well as by change in scores by baseline, for each treatment group.¹

Safety

Safety assessments were conducted regularly throughout the study and included recording vital signs, laboratory and physical examinations, monitoring adverse events (AEs), and ECG and clinical assessments. Safety data were summarised, and no formal statistical analyses were performed. Adverse events (AEs) were graded with the use of the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE).¹

Figure 6.2. Summary of SOLO1 study design



Source: AstraZeneca Clinical Summary, p. 19/47

Protocol Amendments

Protocol amendments are summarized below:

Table 6.4: Summary of protocol amendments in the SOLO1 trial

Number (date of internal approval)	Key details of amendment (Section of this report affected)	Reason for amendment
Amendments made after the start of patient recruitment		
Protocol Amendment 1 5 December 2013	Changed text to include patients who progressed could remain on study treatment (Section 5.1).	Updated to allow patients who had progressed to continue to receive study treatment if, in the opinion of the investigator, it was in the patient's best interest.
	Increased the approximate number of centres participating in this study (Section 2.1).	To clarify the approximate number of centres
	Inclusion of an additional secondary objective of assessing efficacy by TFST, TSST and TDT (Section 4.2, Section 5.5 and Section 5.7.4)	To further assess efficacy
	Clarified that AstraZeneca will pay for Myriad testing and specified that the tumour specimen could only be diagnostic in order to determine the mutation result removed (Section 5.1).	To clarify who was to pay for confirmatory <i>BRCA</i> testing for patients during/post screening and to allow tumour samples to come from a wider range of tumour material collected after original diagnosis was made.
	Table 1 of CSP updated (Not applicable)	Clarification to collection of Myriad <i>gBRCA</i> sample timing. Clarification to urinalysis during screening Part 1. No requirement for BP and pulse to be measured in a supine position. Addition of footnote q to concomitant medications. Clarification to collection of SAE and AE data during screening Part 1.
Amendments made before the start of patient recruitment		
Protocol Amendment 1 5 December 2013	Table 2 of CSP updated (Not applicable)	No requirement for BP and pulse to be measured in a supine position. Clarification of text and location of all required laboratory tests.
	Table 3 of the CSP updated (Section 5.1, Table 2)	No requirement for BP and pulse to be measured in a supine position. Removed duplicated and unnecessary footnotes from urinalysis. Updated to clarify procedures for patients who had progressed and continued to receive study treatment.
	Table 4 of the CSP updated (Section 5.1, Table 3)	Addition of text to clarify visits to take place for patients who remained on treatment post progression and then subsequently discontinued treatment. Addition of resource use in PFS2 and OS follow up to collect data to ensure accurate economic assessment of olaparib. Clarification of subsequent anti-cancer treatment collection.
	Specification that other platinum agents may have been administered to inclusion criterion 5 (Section 5.3.1)	Clarification that other platinum agents may have been administered beside carboplatin or cisplatin.
	Clarification to exclusion criterion 8 (Section 5.3.2)	Clarification of which patients with synchronous endometrial cancer were eligible.
	Revision of methods of statistical analyses (Section 5.7.3, Section 5.7.4.1, Section 5.7.4.2, Section 5.7.4.3, Section 5.7.4.4)	Revised to highlight the key sensitivity analyses in patients whose <i>gBRCAm</i> status was confirmed by the central Myriad test.
	Revision of the analysis of the PFS2 endpoint (Section 5.7.4.1)	Revised to remove the text relating to time to subsequent therapy as a supportive analysis to PFS2.

Number (date of internal approval)	Key details of amendment (Section of this report affected)	Reason for amendment
Protocol Amendment 2 19 December 2014	Addition of the China cohort (Section 2.1, Section 5.1 and Section 5.7.2)	Addition of China patient cohort to allow the originally allocated patients from China to be recruited to the study.
	Changed the type of analysis for FACT-O scores (Section 4.2, Section 4.4, Section 5.5 and Section 5.7.4.7)	Changed to MMRM analysis which is independent of minimal important differences values.
	Revised wording associated with the use of blood samples (Section 5.1)	Revised to correct an inconsistency in wording associated with the use of blood samples collected for <i>gBRC4</i> testing.
	Table 2 of CSP updated (Not applicable)	Clarification for bridging study requirement. Addition of the explanation about necessity of blood samples collection from all consented patients, including <i>BRC4</i> known patients who did not reach randomisation visit.
	Removal of survival and time to second progression assessments from study schedule (Section 5.1)	Clarification of the study design by removal of an assessments added by an error.
	Change in study design to allow continuous collection of Quality of Life data beyond disease progression (Section 5.1)	Additional data collected was to allow more comprehensive comparison of the changes in HRQoL on both arms.
	Clarification to exclusion criterion 17 (Section 5.3.2)	Clarified that patients with persistent toxicities \geq CTCAE Grade 2 (rather than $>$ CTCAE Grade 2) were to be excluded.
	Section 6.4.3 of the CSP (recording of adverse events – post follow-up adverse events) was updated (Not applicable)	To further clarify post follow-up adverse event reporting.

Number (date of internal approval)	Key details of amendment (Section of this report affected)	Reason for amendment
Protocol Amendment 2 19 December 2014	Text regarding evaluation of best overall modified RECIST 1.1 response revised (Section 5.7.4.6)	Text revised for consistency with current AstraZeneca oncology statistical guidance, which states that ORR should only be calculated using data up to the point of any subsequent therapies being used. Text regarding the DCR also removed as the inclusion of this endpoint was no longer required and was not consistent with current AstraZeneca oncology statistical guidance. In addition, the confirmed visit response text was not consistent with modified RECIST 1.1.
	Text regarding the multiplicity strategy for primary and key secondary endpoints revised (Section 12.2.1 of the CSP and Section 5.7)	To clarify the multiple testing procedure.
	Revised text regarding analysis of primary endpoint (Section 5.7.3)	To ensure that the primary analysis is based on stratification data from the randomisation system following the intent-to-treat principle, irrespective of mis-stratification issues, and to include a sensitivity analysis based on eCRF data.
	Revised text regarding analysis of efficacy endpoints PFS and OS (Section 5.7.3 and Section 5.7.4.2)	To correct an error in the text that did not cover the action to be taken if exactly 20 events are observed.
Protocol Amendment 3 19 February 2016	Changed the assessment of PFS in the primary objective from BICR to investigator assessment (Section 4.1, Section 5.5 and Section 5.7.3)	Emerging data suggested that the assumed median PFS for patients with <i>BRC4m</i> ovarian cancer used to design this study may have been underestimated. This in conjunction with the discrepancy rate observed between investigator confirmed progression and the BICR results suggested it may not be possible to obtain the events required for the protocol specified primary endpoint without a change in the protocol design. The assessment of PFS by BICR was added as a sensitivity analysis.

Number (date of internal approval)	Key details of amendment (Section of this report affected)	Reason for amendment
Protocol Amendment 3 19 February 2016	Changed frequency of RECIST assessments and clarified treatment decision point at 108 weeks (Section 5.1 and Section 5.3.4).	Changed frequency of RECIST assessments from up to 120 weeks to 156 weeks (3 years) and added text to clarify the decision to continue treatment at Week 108.
	Revised text describing TOI analyses (Section 5.7.4.7).	TOI improvement rate analysis and time to worsening analysis will no longer be performed.
	Revised text regarding required contraception in female patients and their partners. New Appendix added ("Acceptable Birth Control Methods") (Section 5.3.3)	Reduction of the required period of contraception for females after stopping study treatment from '3 months' to '1 month'.
	Revised wording describing potential clinical interactions of olaparib (Section 5.4.5.2)	To describe possible clinical effects of olaparib on CYP3A4 and UGT1A1.
	Revised text related to storage of biological samples (none)	Adjustment of wording to reflect transition of long-term biological sample storage responsibility from AstraZeneca United Kingdom Biobank to Fisher Bioservices.

a All protocol amendments were approved by AstraZeneca before being submitted to a regulatory authority and/or an IRB/IEC. BICR blinded independent central review; BP blood pressure; **BRCA**m breast cancer susceptibility gene mutated; CSP clinical study protocol; CTCAE Common Terminology Criteria for Adverse Events; DCR disease control rate; eCRF electronic case report form; IEC Independent Ethics Committee; IRB Institutional Review Board; HRQoL Health-Related quality of life; MMRM mixed model for repeated measures; ORR objective response rate; OS overall survival; PFS progression-free survival; PFS2 time from randomisation to second progression; RECIST Response Evaluation Criteria in Solid Tumours; TDT time from randomisation to study treatment discontinuation or death; TFST time to first subsequent therapy or death; TOI Trial Outcome Index; TSST time to second subsequent therapy or death.

Source: EPAR 2019; p. 26-28; Table 9

Funding

The trial was funded by AstraZeneca and Merck. No competing interests were declared by 6 of the 21 authors listed on the manuscript, and two authors declared non-AstraZeneca and non-Merck related potential conflict of interests (COIs). All other authors reported potential COIs related to compensation from AstraZeneca and/or Merck in the form of employment, stock ownership, advisory/medical board fees, lecture fees, travel support, grants, and consultancy fees. Of the 15 authors, 2 were employed directly by AstraZeneca.¹

b) Populations

A total of 391 participants were randomized, with 260 assigned to olaparib and 131 assigned to placebo. The median age was 53.0 years in both treatment arms, ranging from 29 to 82 years in the olaparib arm and 31 to 84 years in the placebo arm.¹ Overall, 36% (n=142) of patients were <50; 50% (n=195) were ≥50 to <65; and 14% (n=54) were ≥65 years of age. The majority of patients were White (n=320; 82%), followed by Asian (n=59; 15%).² Patient disease characteristics are summarized in Table 6.5. In both treatment arms, 82% of patients experienced a CR following first-line platinum therapy and 18% experienced a PR based on IVRS randomization. However, by data recorded in the eCRF, 72.7% of patients in the olaparib arm and 77.1% in the placebo arm had a clinical CR at randomization (defined by normal CA-125 and NED).⁴⁴ Patient disease characteristics were

generally well balanced with respect to ECOG PS, primary tumor location, CA-125 level, and histologic type. Overall, the majority of patients has an ECOG PS of 0 (n=305; 78%); a primary tumor location in the ovary (n=333; 85%); CA-125 level \leq ULN (n=370; 95%); and a serous histologic subtype (n=376; 96%).¹ Imbalanced characteristics included cycles of first-line platinum-based treatment, international Federation of Gynecology and Obstetrics (FIGO) stage, and BRCA mutation. Fewer patients in the olaparib treatment arm reported 6 cycles of treatment (n=198; 76.2%) compared to the placebo arm (n=106; 81%). There were a higher proportion of patients in the olaparib arm (n=58; 22%) that received 7-9 cycles of platinum-based chemotherapy compared to patients who received olaparib (n=24; 18%). More patients in the olaparib group had FIGO stage III (n=220, 84.6%) compared to the placebo group (n=105, 80.2%), with stage FIGO IIIC being the most common in both treatment arms (68.5% and 69.5% in the olaparib and placebo arms, respectively), and more patients in the olaparib arm with FIGO stage IIIB compared to the placebo arm (10.4% compared to 5.3%, respectively).^{1,2} Fewer patients in the olaparib arm compared to the placebo arm had Stage IV disease (15.4% and 19.8%, respectively). Approximately, 25% (n=66) of patients in the olaparib arm had a BRCA2 mutation, which was 6% less patients compared to the placebo arm (n=40; 31%). There were more patients in the olaparib arm with a BRCA1 mutation (n=191; 73%) compared to the placebo arm (n=91; 69%).¹

Table 6.5. Patient disease characteristics in the SOLO1 trial, ITT population

Table 1. Characteristics of the Patients at Baseline.*		
Characteristic	Olaparib Group (N=260)	Placebo Group (N=131)
	<i>no. of patients (%)</i>	
Clinical response after platinum-based chemotherapy†		
Complete response	213 (82)	107 (82)
Partial response	47 (18)	24 (18)
No. of cycles of platinum-based chemotherapy		
4	2 (1)	0
5	2 (1)	1 (1)
6	198 (76)	106 (81)
7	17 (7)	10 (8)
8	18 (7)	7 (5)
9	23 (9)	7 (5)
ECOG performance status		
Normal activity	200 (77)	105 (80)
Restricted activity	60 (23)	25 (19)
Missing data	0	1 (1)
Primary tumor location		
Ovary	220 (85)	113 (86)
Fallopian tube	22 (8)	11 (8)
Peritoneum	15 (6)	7 (5)
Other‡	3 (1)	0
International FIGO stage§		
Stage III	220 (85)	105 (80)
Stage IV	40 (15)	26 (20)
CA-125 level		
≤ULN	247 (95)	123 (94)
>ULN	13 (5)	7 (5)
Missing data	0	1 (1)
Histologic type		
Serous	246 (95)	130 (99)
Endometrioid	9 (3)	0
Mixed serous and endometrioid	5 (2)	1 (1)
BRCA mutation¶		
BRCA1	191 (73)	91 (69)
BRCA2	66 (25)	40 (31)
BRCA1 and BRCA2	3 (1)	0

* Percentages may not total 100 because of rounding. ECOG denotes Eastern Cooperative Oncology Group.

† Complete response was defined as no evidence of disease on imaging (according to modified Response Evaluation Criteria in Solid Tumors, version 1.1) after chemotherapy and a normal CA-125 level. Partial response was defined as a decrease of at least 30% in tumor volume from the start to the end of chemotherapy or no evidence of disease on imaging after chemotherapy but a CA-125 level above the upper limit of the normal range (ULN).

‡ Other tumor locations included a combination of the ovary, fallopian tube, peritoneum, and omentum (in one patient), a combination of the ovary and peritoneum (one patient), and a combination of the ovary and fallopian tube (one patient).

§ International Federation of Gynecology and Obstetrics (FIGO) stage III indicates involvement of one or both ovaries with cytologically or histologically confirmed spread to the peritoneum outside the pelvis or metastasis to the retroperitoneal lymph nodes (or both), and stage IV indicates distant metastasis excluding peritoneal metastasis.

¶ BRCA mutation status was determined centrally (at Myriad or BGI) or locally. For the five patients from China, germline BRCA mutation status was determined in China with the use of the BGI test.

Source: From New England Journal of Medicine, Moore K, Colombo N, Scambia G, et al. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer, Volume No.

c) Interventions

Treatment Duration and Exposure

All treatments were administered as oral tablets. Patients assigned to olaparib received 300mg to be taken twice daily, and patients assigned to placebo received a tablet that matched the appearance of olaparib to be taken twice daily.

The median duration of treatment in the olaparib arm was 24.6 months (range: 0.0-52.0), and 13.9 months (range: 0.2-45.6) in the placebo arm. Cumulative exposure of olaparib over time is summarized in Table 6.6. Up to the first 3 months of treatment, 80.4% of patients received close to the total daily dose (>500 to ≤600 mg) of olaparib, however, by the time participants made it to >12 months, only 67.9% were being treated with close to the total daily dose. A total of 123 (47%) of patients who received olaparib completed the intervention at 2 years compared to 35 (27%) of patients who received placebo.¹ In the olaparib arm, 26 (10%) patients continued to receive intervention beyond 2 years compared to 3 (2%) patients in the placebo arm. Of patients that continued to receive treatment beyond 2 years, 11 (4.2%) in the olaparib arm and 1 (<1%) patient in the placebo arm and received treatment beyond 2 years in error. At the time of data cut-off (May 17th, 2018), 13 (5%) and 1 (1%) in the olaparib and placebo arms, respectively, continued to receive the trial intervention.

Treatment compliance

The percentage of the actual dose intensity delivered relative to the intended dose intensity through to treatment discontinuation, called the relative dose intensity (RDI), was high at a median of 96.2% (range: 39-100) in the olaparib arm. The median RDI was 99.7% (range: 59-100) in the placebo arm.^{1 1}

Table 6.6. Cumulative exposure (total daily dose) of olaparib over time in the SOLO1 trial

Mean olaparib total daily dose (mg)	Number (%) of patients by time period				
	Up to 3 months (N=260)	>3 to ≤6 months (N=235)	>6 to ≤9 months (N=216)	>9 to ≤12 months (N=204)	>12 months (N=193)
>500 to ≤600	209 (80.4)	169 (71.9)	144 (66.7)	140 (68.6)	131 (67.9)
>400 to ≤500	36 (13.8)	30 (12.8)	41 (19.0)	33 (16.2)	35 (18.1)
≤400	15 (5.8)	36 (15.3)	31 (14.4)	31 (15.2)	27 (14.0)

Source: From New England Journal of Medicine, Moore K, Colombo N, Scambia G, et al. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer, Volume No. 379, Issue 26, Page 24. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society., Table S4 in supplementary

Previous Anticancer Therapies and Procedures

Previous first-line cytotoxic chemotherapy treatments received by patients were reported. The majority of patients received a previous platinum-based regimen containing carboplatin (n=356; 91.0%) and some patients received cisplatin (n=78; 19.9%), and almost all patients received taxane therapy with paclitaxel (n=383; 98.0%).¹

In both treatment arms, there were a similar proportion of patients who had any debulking surgery performed prior to randomisation (98.2% overall). There were a similar proportion of patients in both treatment arms by type of debulking surgery, and overall 63% had upfront debulking surgery and 35% had interval debulking surgery, and only 1.8% of patients did not have any debulking surgery.²

Concomitant Medications

No other anti-cancer therapy, including chemotherapy, immunotherapy, hormonal therapy (with the exception of hormone replacement therapy), radiotherapy, biological therapy, or other novel agent, was permitted during the study. Live virus and bacterial vaccines were also prohibited during the study treatment and up to the 30 day follow-up period following treatment discontinuation. Natural and herbal remedies were discouraged, however, were to be recorded as concomitant medications if used. Olaparib can inhibit CYP3A4 and UGT1A1, and there can be clinically significant interactions with other substrates of these enzymes. Substrates of CYP3A4 and UGT1A1 were to be administered with caution, in addition to CYP3A4 inducers, and if patients took any of these the wash-out period was 1 week prior to starting study treatment. Warfarin and subcutaneous heparin was permitted during the study. Palliative radiotherapy was permitted for the treatment of pain of bony metastases present at baseline, if in the opinion of the investigator, these were not indicative of clinical PD during the study period. For palliative radiotherapy, study treatment was discontinued for a minimum of 3 days, and restarted within 4 weeks if bone marrow toxicity had recovered.¹

Subsequent Interventions

Subsequent therapies (any line) are outlined in Table 6.7. Almost double the proportion of patients had a subsequent therapy in the placebo arm (n=94; 71.8%) compared to the olaparib arm (n=91; 35.0%). The most common subsequent therapy in both arms was platinum chemotherapy, received by 22.3% (n=58) and 38.2% (n=50) of patients in the olaparib and placebo arms, respectively. A higher proportion of patients in placebo arm received a subsequent PARP inhibitor (n=49; 37.4%) compared to the olaparib arm (n= 20; 7.7%). Crossover to olaparib was not permitted, however it could be received outside of the trial through other clinical trials and commercially available products. Olaparib as a subsequent PARP inhibitor was received by 33.6% (n=44) of patients in the placebo arm and 5% (n=13) of patients in the olaparib arm. PARP inhibitors were received as a first subsequent therapy by 25.2% of patients in the placebo arm and 3.8% of patients in the olaparib arm.^{2 8}Subsequent PARP inhibitors by line of therapy are outlined in Table 6.8.

Table 6.7. Post-treatment subsequent therapies by treatment arm in the SOLO1 trial, ITT population

	Number (%) of patients		
	Olaparib 300 mg bd (N=260)	Placebo (N=131)	Total (N=391)
Total	91 (35.0)	94 (71.8)	185 (47.3)
Platinum chemotherapy	58 (22.3)	50 (38.2)	108 (27.6)
Platinum in combination with bevacizumab	22 (8.5)	15 (11.5)	37 (9.5)
PARP inhibitor	20 (7.7)	49 (37.4)	69 (17.6)
Any other chemotherapy regimen (excluding platinum or bevacizumab containing)	35 (13.5)	26 (19.8)	61 (15.6)
Other bevacizumab containing regimen	9 (3.5)	12 (9.2)	21 (5.4)
Other investigational agents	4 (1.5)	3 (2.3)	7 (1.8)
Hormonal agent	0	4 (3.1)	4 (1.0)

Patients may appear under more than one subsequent treatment type.

To note, Table 11.2.4.3 indicates that 93 patients in the placebo arm received a subsequent cancer therapy rather than the 94 presented in this table. This is because Table 12.2.4.3 excludes the patients with missing medication start dates and the patient who did not receive any study medication in the placebo arm.

bd twice daily; FAS Full Analysis Set; PARP polyadenosine 5' diphosphoribose polymerase.

Source: EPAR 2019; p. 41/109; Table 24

Table 6.8. Subsequent PARP inhibitor by line of therapy, ITT population

	Number (%) of patients		
	Olaparib 300 mg bd (N=260)	Placebo (N=131)	Total (N=391)
Received PARP inhibitor	20 (7.7)	49 (37.4)	69 (17.6)
First subsequent therapy	10 (3.8)	33 (25.2)	43 (11.0)
Second subsequent therapy	5 (1.9)	11 (8.4)	16 (4.1)
Third subsequent therapy	4 (1.5)	4 (3.1)	8 (2.0)
Fourth subsequent therapy	0	2 (1.5)	2 (0.5)
Fifth subsequent therapy	2 (0.8)	0	2 (0.5)
Patients who subsequently received olaparib	13 (5.0)	44 (33.6)	57 (14.6)

bd twice daily; FAS Full Analysis Set; PARP polyadenosine 5' diphosphoribose polymerase.

Source: EPAR 2019 ; p. 41/109 ; Table 25

d) Patient Disposition

The patient disposition flow diagram is outlined in Figure 6.3. Of 1084 patients enrolled into the study, 674 did not meet eligibility criteria, 14 declined to participate, 3 were lost to follow-up, and 2 died. The most common inclusion criteria that was not met was a documented BRCA 1/2 mutation predicted to be deleterious or suspected deleterious (n=504).⁴³ A total of 391 patients underwent randomisation, with 260 assigned to received olaparib and 131 assigned to receive placebo. All 260 patients received their assigned treatment with olaparib, and 130 patients received their assigned treatment with placebo. One patient did not receive placebo due to early withdrawal.¹

As of the May 17th, 2018, data cut-off date, 123 (47.3%) patients in the olaparib arm and 35 (26.9%) patients in the placebo arm completed the intervention at 2 years as per protocol. In the olaparib arm, 51 (19.6%) discontinued treatment due to PD; 30 (11.5%) due to adverse events (AEs); 22 (8.5%) voluntarily withdrew; 11 (4.2%) discontinued for other reasons; 6 (2.3%) met discontinuation criteria; 3 (1.2%) had severe protocol deviations; 1 (0.4%) discontinued for an unknown reason. In the placebo arm, 78 (60.0%) discontinued due to PD; 9 (6.9%) for other reasons; 3 (2.3%) due to AEs, 2 (1.5%) voluntarily withdrew, 1 (0.8%) met discontinuation criteria, and 1 (0.8%) was lost to follow-up. More participants in the placebo arm discontinued treatment due to PD in the placebo arm compared to the olaparib arm, however more patients voluntarily withdrew from olaparib compared to placebo. Thirteen (5.0%) patients in the olaparib arm and 1 (0.8%) patient in placebo arm was still receiving treatment as of the data cut-off date.¹

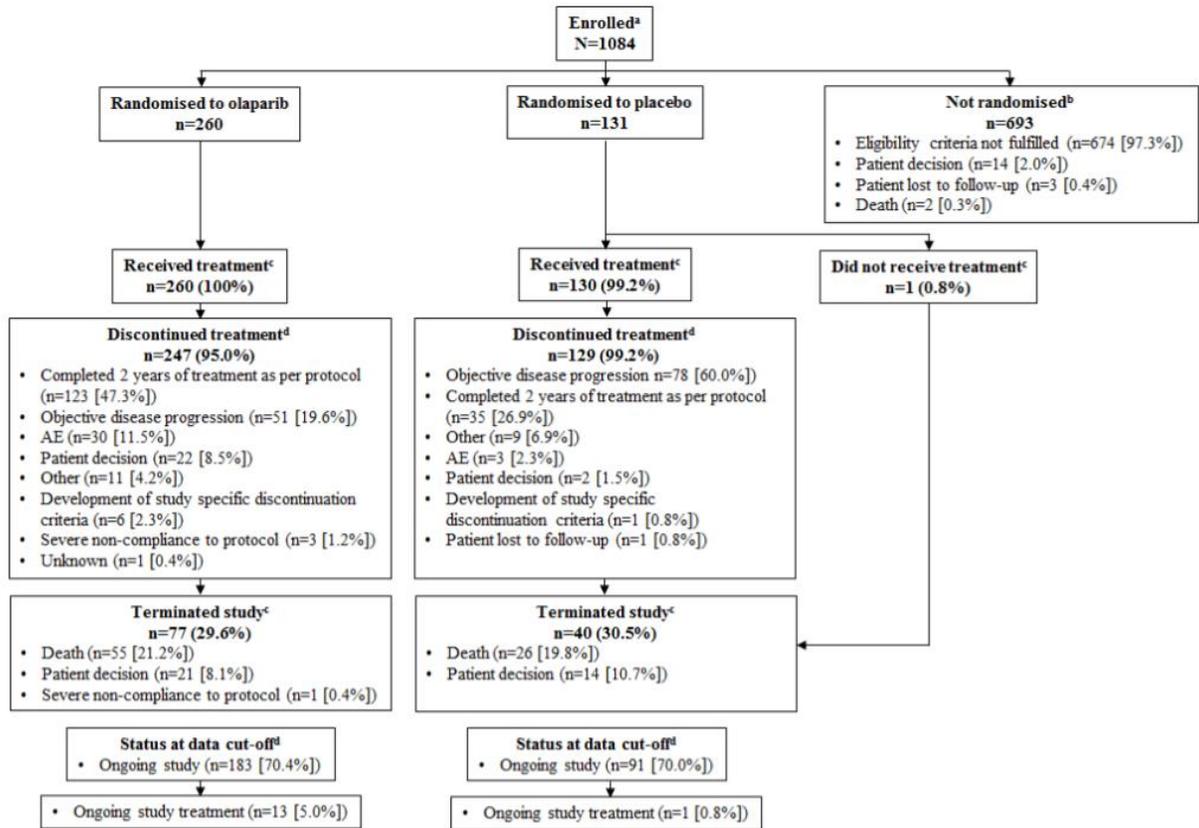
A total of 77 (29.6%) of patients terminated the study in the olaparib arm due to death (n=55; 21.2%), patient decision (n=21; 8.1%), or severe non-compliance to the protocol (n=1; 0.4%). A total of 40 (30.5%) patients terminated the study in the placebo arm due to death (n=26; 19.8%) or patient decision (n=14; 10.7%).^{2,9}

Protocol Deviations

In the olaparib arm, 37 (14.2%) patients had at least 1 important protocol deviation compared to 10 (7.6%) patients in the placebo arm. In the olaparib arm, having a RECIST scan outside of a scheduled visit window on >2 occasions was the most

common reason for a protocol deviation (n=19; 7.3%), followed by severe non-compliance with treatment (n=5; 1.9%) and baseline RECIST scan >28 days before study treatment started (n=5; 1.9%). In the placebo arm, the most common protocol deviations included patients receiving any systemic chemotherapy or radiotherapy (aside from palliative therapy) within 3 weeks prior to randomization (n=3; 2.3%), followed by RECIST scans outside of scheduled visits (n=2; 1.5%), abnormal organ and bone marrow function measured within 28 days of randomization (n=2; 1.5%), and use of prohibited concomitant medication or therapies while receiving study treatment (n=2; 1.5%; note: one patient is included in this category in error).^{2,8} See Table 6.9 for more details.

Figure 6.3. SOLO1 participant disposition flow diagram



Source: EPAR 2019; p. 23/109; Figure 2

Table 6.9: Important protocol deviations in the SOLO1 trial, ITT population

	Number (%) of patients		
	Olaparib 300 mg bd (N=260)	Placebo (N=131)	Total (N=391)
Number of patients with at least 1 important deviation ^a	37 (14.2)	10 (7.6)	47 (12.0)
RECIST scans outside of a scheduled visit window on >2 occasions	19 (7.3)	2 (1.5)	21 (5.4)
Baseline RECIST scan >28 days before study treatment was started	5 (1.9)	1 (0.8)	6 (1.5)
Patients receiving any systemic chemotherapy or radiotherapy (except for palliative reasons) within 3 weeks prior to study treatment (or longer period depending on defined characteristics of agents used)	2 (0.8)	3 (2.3)	5 (1.3)
Severe non-compliance with treatment	5 (1.9)	0	5 (1.3)
Method of tumour assessment other than MRI or CT scan used	2 (0.8)	1 (0.8)	3 (0.8)
Patients must have normal organ and bone marrow function measured within 28 days of randomisation	1 (0.4)	2 (1.5)	3 (0.8)
The subject took concomitant medications or therapies prohibited whilst subject was receiving study medication	1 (0.4)	2 (1.5) ^b	3 (0.8)
Patients did not complete 1 st line platinum-containing therapy (intravenous or intraperitoneal) prior to randomisation, and did not meet the further conditions described in the protocol	2 (0.8)	0	2 (0.5)
Pre-treatment CA-125 criterion - 1 st value within ULN, patient eligible for randomisation, 2 nd sample not required. - 1 st value >ULN then 2 nd assessment performed ≥7 days after 1 st . If ≥15% of 1 st , patient not eligible	2 (0.8)	0	2 (0.5)
ECOG performance status not 0-1	1 (0.4)	0	1 (0.3)

^a Important deviations before the start of treatment and during treatment.

^b Patient E7855015, who was randomised to the placebo arm, is included in this category in error as she withdrew before receiving any study medication.

Note that the same patient may have had more than 1 important protocol deviation.

Source: EPAR 2019; p. 30/109; Table 10

e) Limitations/Sources of Bias

Key limitations and sources of bias include:

- There were a number of baseline characteristics that were imbalanced, which included cycles of first-line platinum-based treatment, international Federation of Gynecology and Obstetrics (FIGO) stage, and BRCA mutation. There were more patients in the olaparib arm (22% vs. 18% in the placebo arm) that received 7-9 cycles of platinum-based therapy, which could indicate these patients required more treatment in order to achieve a response. Through IVRS, it was recorded 82% of patients in both arms had a CR to prior therapy, whereas the eCRF indicated only 72.7% in the olaparib arm and 77.1% in the placebo arm had a CR to previous treatment, thus supporting that patients in the olaparib arm may have required more

treatment to achieve a response to prior therapy.^{1,44} Research suggests that patients who receive more than 6 cycles of chemotherapy as consolidation chemotherapy may not experience improved outcomes (OS and PFS) and may result in unnecessary, additional toxicities.⁴⁶ Thus, patients may have had more severe disease and were less responsive to chemotherapy if additional cycles of chemotherapy were required to achieve a response, and may have had a worse health status overall due to increased toxicities associated with a longer duration of first-line chemotherapy in the olaparib arm. Additionally, there were more patients in the placebo arm with Stage IV disease (20% vs. 15% in the olaparib arm), which is indicative of potentially poorer prognosis in the placebo arm.¹ Finally, there were more patients with a BRCA2 mutation in the placebo arm (31% vs. 25% in the olaparib arm), which may be associated with a better prognosis (specifically, OS).^{1,47} The combination of these imbalances may have confounded the results in an unknown direction.

- Though patients with germline or somatic mutations were eligible for participation in the study, it was found that 99.2% of patients had a centrally confirmed germline BRCA 1/2 mutation, and thus the study results may not be generalizable to patients with only somatic BRCA mutations.¹ In addition, the majority of patients overall had a serous histology (96%) with a primary tumor location in the ovary (85%), and thus the study results may not be generalizable to endometrioid or other primary tumor locations (i.e., fallopian tube and primary peritoneal) included in the study.¹
- There were a larger proportion of patients that had a subsequent therapy in the placebo arm (71.8 %) compared to the olaparib arm (35.0%) arm, with a higher proportion of patients in the placebo arm receiving a subsequent PARP inhibitor (37.4% vs. 7.7%, for the placebo and olaparib arms, respectively). The type and number of subsequent therapies received in each arm may have confounded the results in an unknown direction. It was noted the benefit of olaparib was observed despite imbalances between the first subsequent therapy received between treatment arms, specifically, 3.8% of olaparib patients vs. 25.2% of placebo patients received a PARP inhibitor as the first subsequent therapy.^{2,8}
- Investigator-assessed outcomes were used for the primary analyses, which may be subject to bias. However, the amount of bias is considered minimal, as the submitter conducted sensitivity analyses using a BICR and the results were largely consistent with the investigator-assessed results.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

Efficacy analyses were performed using the intention-to-treat (ITT) population, which includes all patients who were randomised, regardless of treatment received. A total of 391 patients were included in the ITT population. As of the data cut-off date of May 17th, 2018, the median duration of follow-up was 40.7 months (IQR: 34.9, 42.9) in the olaparib arm, and 41.2 months (IQR: 32.2, 41.6) in the placebo arm.¹

Central Germline and Tumor BRCA Testing

In total, 383 of the 391 (98.0%) patients had a centrally confirmed germline BRCA1/2 mutation after randomization with the Myriad testing.¹ In the olaparib arm, 1 (0.4%) patient had a germline BRCA variant of unknown significance (VUS) and 2 (0.8%) patients had germline BRCA wildtype. There were 4 patients in the olaparib arm and 1 patient in the placebo arm that had missing Myriad germline BRCA mutation results (patients tested by BGI in China and were confirmed to have a germline mutation).^{1,2}

A total of 324 of the 391 (82.9%) patients had a centrally confirmed Foundation Medicine tumor BRCA mutation after randomisation.¹ There were 5 patients that had a BRCA variant of unknown significance. There were 12 patients that had tumor BRCA wildtype.¹ A total of 50 (12.8%) patients were missing tumor BRCA status, with 33 (12.7%) and 17 (13.0%) patients in the olaparib and placebo arms, respectively.² Of these 50 patients, 23 did not have a sample available and 27 patients failed tumor BRCA testing due to insufficient quantity of extracted DNA, sequencing metrics, or computational metrics for variant calling.¹

The two patients with germline BRCA wildtype by Myriad testing were confirmed to have a Foundation Medicine tumor BRCA mutation, and thus these two patients had somatic BRCA mutations.¹

Primary Endpoint

Progression-Free Survival

A total of 198 investigator-assessed PD events or death occurred at the time of the primary analysis (~50% maturity), with a total of 102 (39.2%) PFS events in the olaparib arm and 96 (73.3%) PFS events in the placebo arm. Overall, 51.5% of patients in the olaparib arm compared to 24.4% of patients in the placebo arm were progression free at the time of the primary analysis.² The K-M estimate of the rate of PFS at 3 years was 60% in the olaparib arm and 27% in the placebo arm.¹ The median PFS in the olaparib arm was not reached, and was 13.8 months (95% CI: 11.1, 18.2) in the placebo arm. There was a 70% reduction in the risk of disease progression or death in the olaparib arm compared to the placebo arm (HR: 0.30; 95% CI: 0.23, 0.41; p<0.0001). The BICR assessment of PFS was consistent with the primary analysis (HR: 0.28; 95% CI: 0.20, 0.39; p<0.0001), however the testing was not controlled for multiplicity and thus is exploratory in nature.¹ The K-M curve of investigator-assessed PFS is shown in Figure 6.4. Overall, there was 15% discordance between investigator and central reviews declaring PD.²

Subgroup analyses of PFS were consistent with the overall trial results, with a clinically meaningful reduction in the risk of PD or death observed across all pre-specified subgroups as shown in Figure 6.5.¹

Results of the pre-specified sensitivity analyses are presented in Table 6.10. All results were consistent with the primary analysis of PFS.^{1,2} The sensitivity analysis for ascertainment bias, was conducted and consistent with the primary analysis of PFS (not shown in Table).¹ The deviation bias sensitivity analysis was not conducted, as none of the pre-specified protocol deviations that could affect efficacy occurred in >10% of patients.^{1,2}

In addition, the sensitivity analyses of PFS by investigator assessment using the 383 Myriad germline BRCA mutated patients (HR: 0.30; 95% CI: 0.22, 0.40; <0.0001), and using the 324 tumor BRCA mutated patients confirmed by Foundation Medicine (HR: 0.28; 95% CI: 0.21, 0.39; P<0.0001) was consistent with the primary analysis of PFS.²

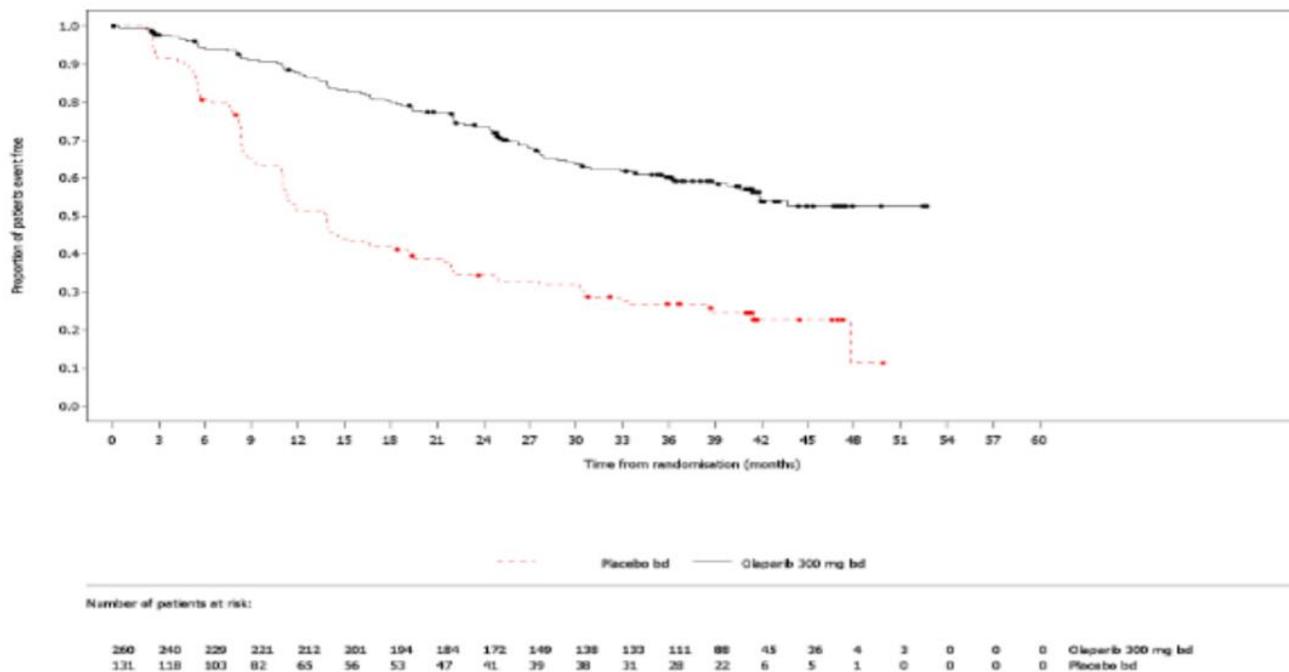
The analysis of PFS24 was also conducted but is not reported here. It was noted that the stratified KM estimate of PFS24 in the placebo arm may be underestimated as the Greenwood variance estimator tends to underestimate variance in the tails of the survival distribution.⁸

An additional analysis was conducted to investigate PFS by BRCA mutation type (BRCA1 vs. BRCA2). The results were consistent with the primary PFS results, although suggestive of enhanced benefit for BRCA2 mutation patients. The median PFS was 41.4 months in the olaparib arm (n=191) compared to 13.8 months in the placebo arm (n=91) for BRCA1 mutated patients. There was a 59% reduction in the risk of progression or death (HR: 0.41; 95% CI: 0.30, 0.56) in BRCA1 mutated patients. For BRCA2 mutated patients, the median PFS was not reach in the olaparib arm (n=66) and was 13.8 months in the placebo arm (n=40). There was an 80% reduction in the risk of progression or death in the olaparib arm compared to the placebo arm for BRCA2 mutated patients (HR: 0.20; 95% CI: 0.10, 0.37). The percentage of patients who were progression-free at 3 years in the olaparib arm was 53% compared to 26% in the placebo arm for BRCA1 mutated patients. In contrast, 80% were progression-free in the olaparib arm in the BRCA2 mutated patient subgroup compared to 29% in the placebo arm.⁴

Analyses of PFS by timing of surgery (upfront and interval surgery subgroups), presence of residual tumor following surgery (no residual disease and residual disease subgroups), and response status (complete response and partial response subgroups) after completion of SOLO1 were also conducted. All results were consistent with the primary analysis of PFS. Of note, olaparib patients relative to placebo patients with no residual disease may have had enhanced outcomes in terms of PFS with a 67% reduction in the risk of progression or death (HR: 0.33; 95% CI: 0.23, 0.46) compared to olaparib patients relative to placebo patients with residual disease where there was a 56% reduction in the risk of progression or death (HR: 0.44; 95% CI: 0.25, 0.77).⁵

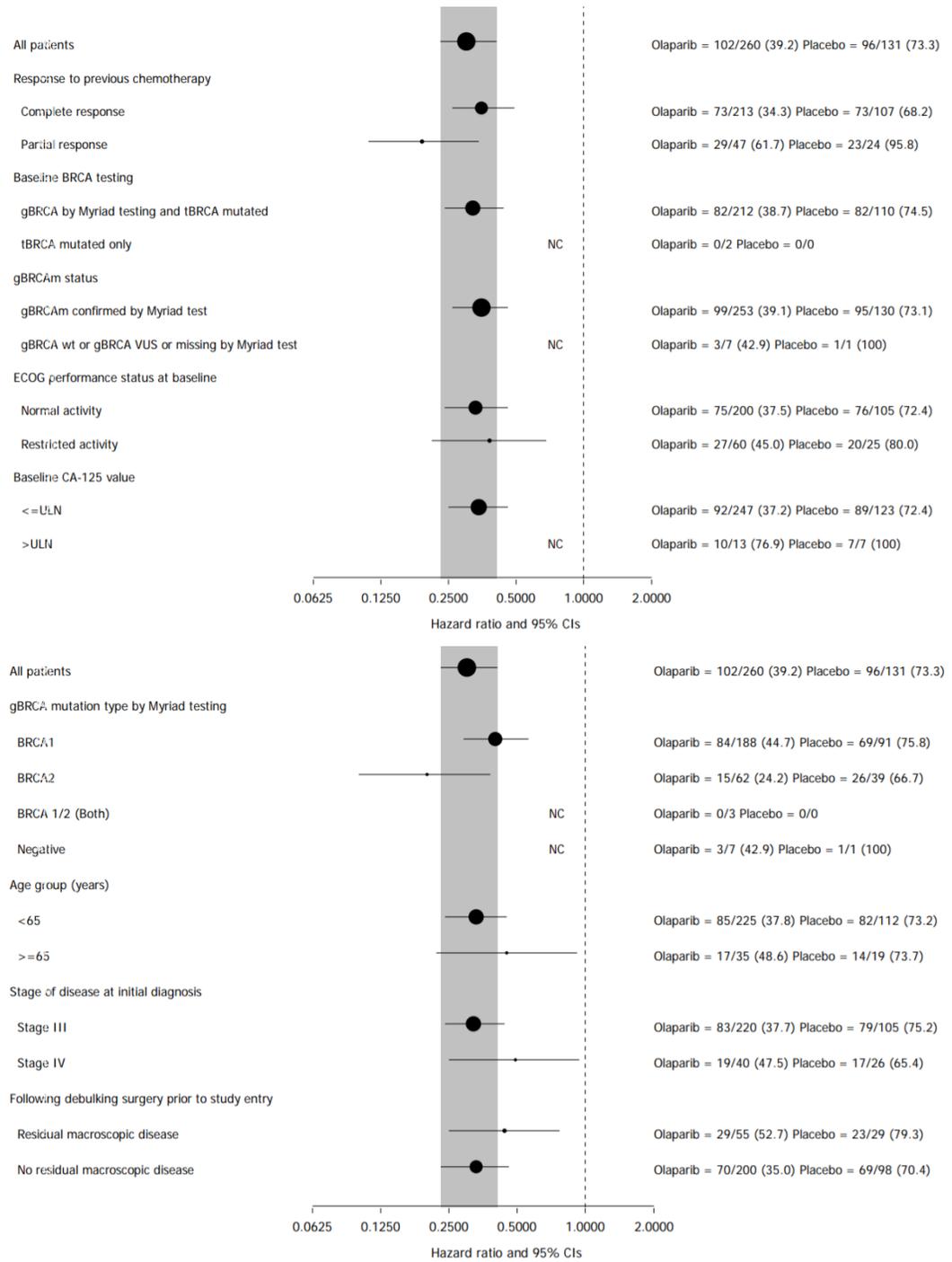
All subgroup and sensitivity analyses are exploratory in nature as the study was not powered to detect differences in these outcomes.

Figure 6.4: Kaplan-Meier Curves for investigator-assessed progression-free survival in the SOLO1 trial, ITT population



Source: EPAR 2019; p. 34/106; Figure 4

Figure 6.5: Subgroup analyses of progression-free survival in the SOLO1 trial, ITT population



Source: EPAR 2019; p. 46-47/109; Figure 12

Table 6.10: Pre-specified sensitivity Analyses for progression-free survival in the SOLO1 trial, ITT population

	Number (%) of patients with events Events:Patients	Median PFS (months)	HR	95% CI	p-value
Sensitivity analysis: evaluation time bias	Olaparib: 102 (39.2)	NR	0.31	0.23, 0.41	<0.0001
	Placebo: 96 (73.3)	12.4			
Sensitivity analysis: attrition bias	Olaparib: 102 (39.2)	49.9	0.31	0.23, 0.41	<0.0001
	Placebo: 93 (71.0)	13.8			
Sensitivity analysis: using the eCRF stratification variable	Olaparib: 102 (39.2)	NR	0.33	0.25, 0.44	<0.0001
	Placebo: 96 (73.3)	13.8			
Sensitivity analysis: to assess possible informative censoring (using BICR)	Olaparib: 107 (41.2)	46.9	0.31	0.24, 0.42	<0.0001
	Placebo: 96 (73.3)	11.1			
Sensitivity analysis: estimating HR using the stratified log rank test	Olaparib: 102 (39.2)	NR	0.25	0.18, 0.34	<0.0001
	Placebo: 96 (73.3)	13.8			
Additional analysis: based on earliest progression of investigator/BICR assessment of progression	Olaparib: 107 (41.2)	NR	0.31	0.24, 0.42	<0.0001
	Placebo: 96 (73.3)	11.1			

bd twice daily; BICR blinded independent central review; CI confidence interval; eCRF electronic case report form; FAS Full Analysis Set; HR hazard ratio; NR not reached; PFS progression free survival; RECIST Response Evaluation Criteria in Solid Tumours.

Data derived from Table 11.2.1.3, Table 11.2.1.4, Table 11.2.1.15, Table 11.2.1.16, Table 11.2.1.17 and Table 11.2.1.18.

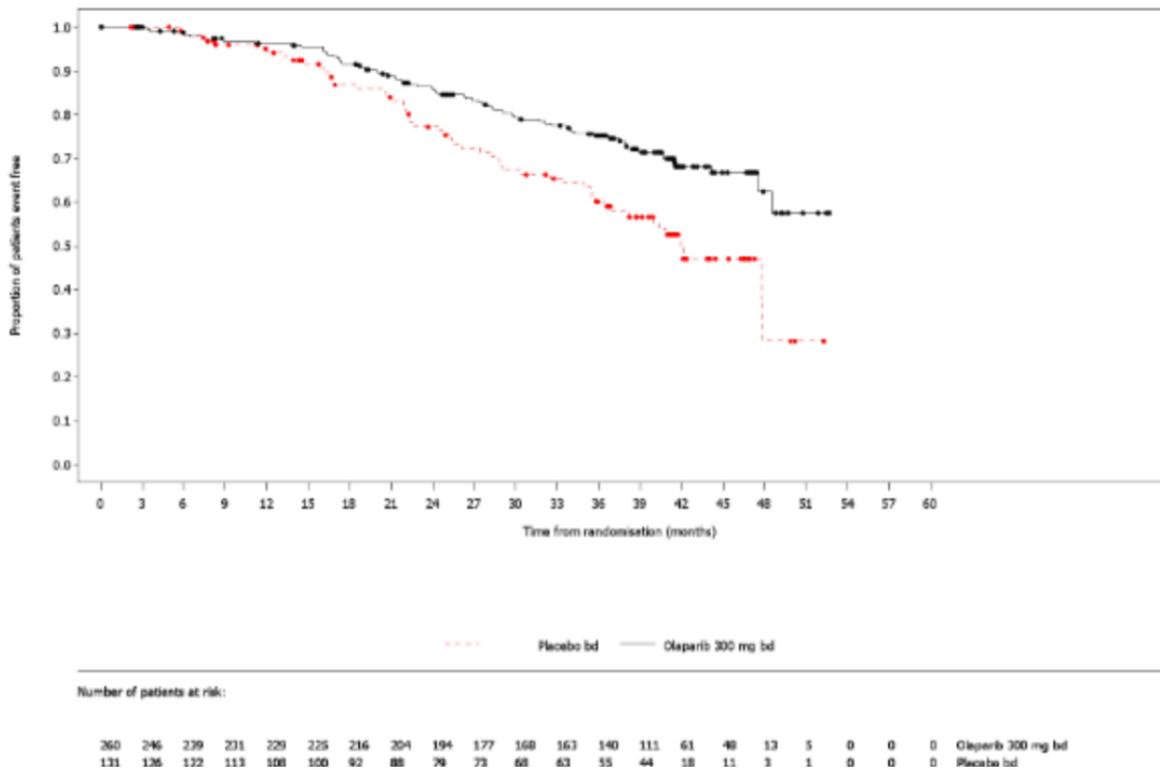
Source: EPAR 2019; p. 45/109; Table 32

Secondary Endpoints

Second Progression-Free Survival (PFS2)

At the time of data cut-off, 121 PFS2 events had occurred (69 [26.5%] in the olaparib arm, 52 [39.7%] in the placebo arm). Overall, 61.2% of patients in the olaparib arm vs. 40.5% in the placebo arm were second progression free at the time of the analysis.² PFS2 was performed at 31% data maturity, and the K-M estimates of the rate of PFS2 at 3 years was 75.1% in the olaparib arm and 60.2% in the placebo arm. There was a reduction in the risk of second PD or death of 50% in the olaparib arm compared to the placebo arm (HR: 0.50; 95% CI: 0.35, 0.72; $p < 0.001$), as illustrated in Figure 6.6. The median PFS2 was not reached in the olaparib arm and was 41.9 months (95% CI: 36.5, 47.9) in the placebo arm.^{1,2}

Figure 6.6. Kaplan-Meier curve for second progression-free survival in the SOLO1 trial, ITT population

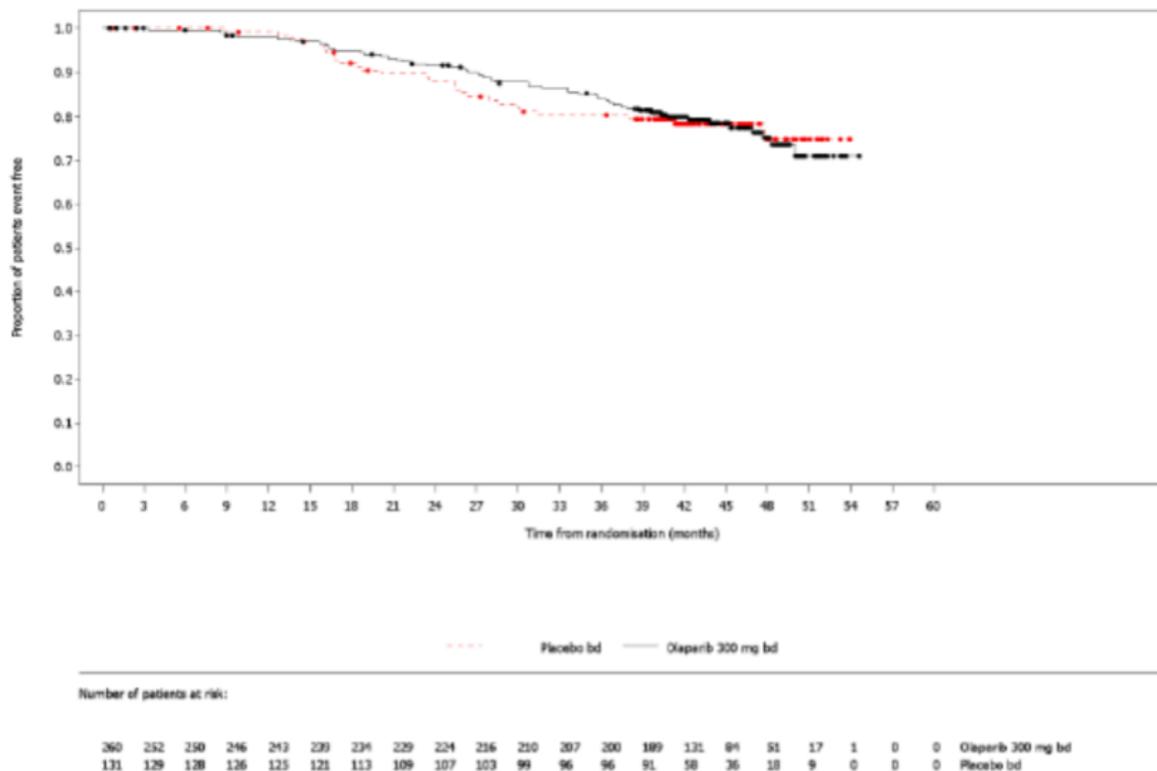


Source: EPAR 2019; p. 36/109; Figure 5

Overall Survival (OS)

At the time of data cut-off, the interim OS data were immature (~21% maturity), and 70.4% of patients in the olaparib arm and 69.5% in placebo arm were alive. A total of 82 events (55 in the olaparib arm and 27 in the placebo arm) occurred.² The K-M estimate of the rate of freedom from death at 3 years was 84% in the olaparib arm and 80% in the placebo arm. There was no difference in the risk of death between olaparib and placebo (HR: 0.95; 95% CI: 0.60, 1.53), and the K-M curve for OS is illustrated in Figure 6.7.¹ The median OS was not reached in either treatment arm.²

Figure 6.7: Kaplan-Meier curve for overall survival in the SOLO1 trial, ITT population



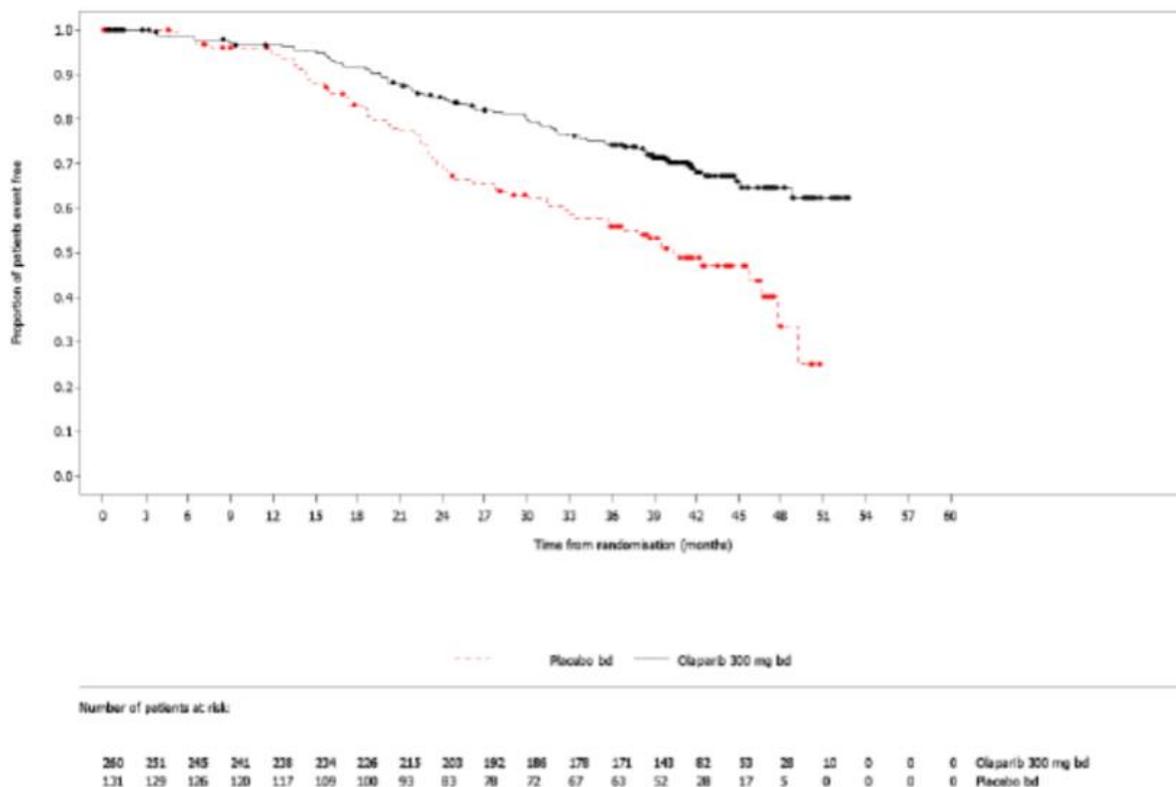
Source: EPAR 2019; p.37/109; Figure 6

Time from randomisation to the start of first subsequent therapy or death (TFST)

The median TFST was 51.8 months (95% CI: 44.3, NR) in the olaparib arm compared to 15.1 months (95% CI: 12.7, 20.5) in the placebo arm (Figure 6.8).² There was a 70% reduction in the risk of earlier TFST in the olaparib arm compared to the placebo arm (HR: 0.30; 95% CI: 0.22, 0.40, p<0.0001).¹ The sensitivity analyses using centrally confirmed BRCA mutated patients (by both Myriad and Foundation Medicine testing) were consistent with the results using the ITT population.² This analysis was not controlled for multiplicity.

Figure 6.8. Time from to the start of first subsequent therapy or death in the SOLO1 trial, ITT population

Figure 6.9. Time from to the start of second subsequent therapy or death in the SOLO1 trial, ITT population

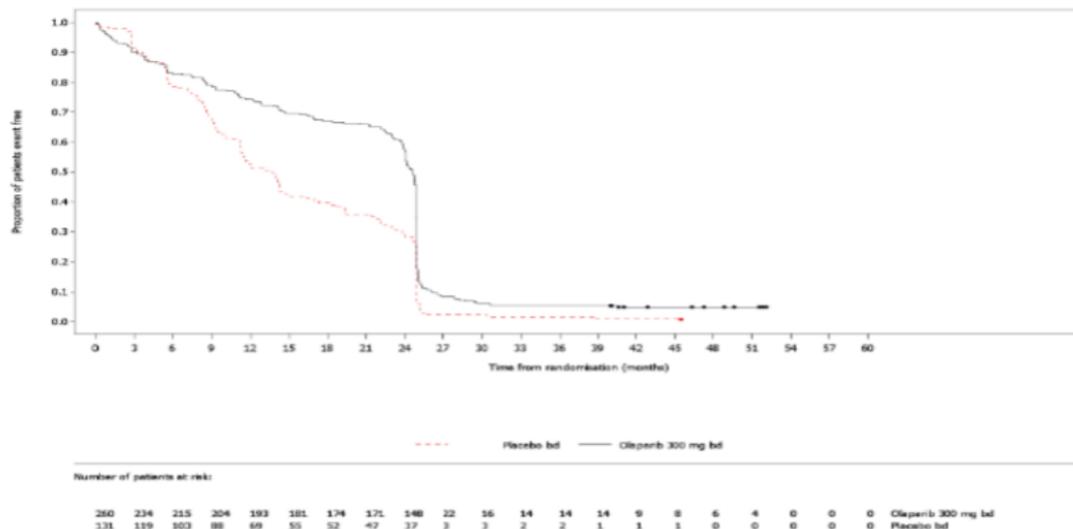


Source: EPAR 2019; p. 40/109; Figure 9

Time from randomisation to study treatment discontinuation or death (TDT)

The median TDT was 24.6 months (95% CI: 24.0, 24.8) for patients in the olaparib arm and 13.8 months (95% CI: 11.2, 16.4) for patients in the placebo arm, with a 37% reduction in the risk of discontinuing treatment or death associated with the olaparib arm (HR: 0.63; 95% CI: 0.51, 0.79; p<0.0001).³ Twenty-six (10.0%) patients in the olaparib arm and three (2.3%) patients in the placebo arm continued treatment after 2 years on study, which explains why the time to treatment discontinuation extends beyond 2 years and the most common reason for discontinuation in the olaparib arm was completion of 2 years of treatment (47.3%).² As illustrated in Figure 6.10, this treatment discontinuation is reflected in the drop in patients at the 24 month mark, and the difference between the olaparib arm and placebo arm beyond this time point generally reflects time to death, which is minimal between arms based on visual inspection and consistent with the non-significant overall survival results. This analysis was not controlled for multiplicity.

Figure 6.10. Time from randomisation to study treatment discontinuation or death in the SOLO1 trial, ITT population



Source: EPAR 2019; p. 37/109; Figure 7

Time to earliest progression by RECIST, CA-125, or death

The time to earliest PD by RECIST, CA-125, or death was not reached in the olaparib arm, and was 12 months (95% CI: 10.8, 16.6) in the placebo arm.³ There was a 70% reduction in the risk of PD, as defined by earliest RECIST, CA-125, or death event, in the olaparib arm compared to the placebo arm, which was consistent with the primary analysis of PFS (HR: 0.30; 95% CI: 0.23, 0.40; $p < 0.0001$).² This analysis was not controlled for multiplicity.

Best overall response

There were 80 patients with evidence of disease (target or non-target lesions) at baseline, with 54 patients in the olaparib arm and 26 patients in the placebo arm. Among those with evidence of disease, an ORR (CR or PR) of 42.6% (n=23) was achieved in patients in the olaparib arm compared to 23.1% (n=6) of patients in the placebo arm. In the olaparib arm, 27.8% (n=15) experienced a CR and 14.8% (n=8) experienced a PR compared to patients in the placebo arm where 11.5% (n=3) experienced a CR and 11.5% experienced a PR. In patients in the olaparib arm with an objective response (CR or PR), median time from randomisation to the onset of response was 10.8 months, and the median duration of response was 28.2 months compared to a median onset of response of 5.4 months in the placebo arm and median duration of response of 8.6 months.²

Additional Analyses

An additional China cohort was planned as per the SOLO1 trial protocol to evaluate the safety and efficacy of olaparib in Chinese patients. The sample size was planned for approximately 53 patients, which provided a 90% chance to observe an HR < 1 , assuming a true HR of 0.62. The primary endpoint was investigator-assessed PFS by modified RECIST 1.1, with a sensitivity analysis of PFS by BICR. A total of 64 randomized patients received study treatment, with 44 in the olaparib arm and 20 patients in the placebo arm. Median PFS was not reached in the olaparib arm and was 9.3 months in the placebo arm as assessed by both investigator (data at

48% maturity) and BICR (data at 39% maturity). The most common AEs in the olaparib arm were nausea (n=28, 63.6%), anemia (n = 25, 56.8%), and vomiting (n = 18, 40.9%). Grade ≥ 3 AEs occurred in 56.8% of olaparib patients compared to 30.0% of placebo patients. The most common grade ≥ 3 AE was anemia (n = 16, 36.4%).⁷ Anemia at any grade and grade ≥ 3 in the olaparib arm occurred at a higher rate in the China cohort than in the global trial (39% of patients in the olaparib arm had any grade anemia and 22% had grade ≥ 3 anemia).⁶ Olaparib dose interruptions occurred in 56.8% of patients compared to 30.0 % of patients in the placebo arm. Similarly, a higher proportion of dose reductions and discontinuations occurred in 27.3% and 6.8% of patients in the olaparib arm, compared to 10% and 0% in the placebo arm.⁷

Health related quality of life (HrQOL)

The compliance rates for the planned on-treatment visits by FACT-O were high (above 80%) from baseline to week 97 (~2 years).

The baseline TOI scores were high for both treatment arms, with a mean score of 73.6 in the olaparib arm and 75 in the placebo arm. Similarly, the baseline FACT-O scores were high, with a mean score of 113.5 in the olaparib arm and 115.8 in the placebo arm. There were no differences between treatment arms in baseline scores. The estimated mean change from baseline in the olaparib arm to 24 months was stable with a change of 0.3 (95% CI: -0.72, 1.32). The estimated mean change from baseline in the placebo arm to 24 months was 3.3 (95% CI: 1.84, 4.76), which showed a small improvement over time. The estimated difference between treatment arms in mean change from baseline was -3.00 (95% CI: -4.88, -1.2)), which indicated a small worsening of quality of life with olaparib that was statistically significant, but not considered clinically relevant. The sensitivity analysis using AUC summary of TOI score over all visits up to 24 months supported the primary analysis of TOI score of no worsening or deterioration of TOI of olaparib relative to placebo in HRQoL.²

Exploratory Outcomes - EuroQoL - 5 dimensions, 5 levels (EQ-5D-5L)

There was no worsening or deterioration of patients in the olaparib arm relative to patients in the placebo arm as measured by the weighted health index score or by the VAS to week 97.⁸

Harms Outcomes

The safety analysis set (SAS) included all patients who received at least one dose of the study drug, olaparib or placebo, based on randomisation. In cases where patients randomised to olaparib or placebo but were erroneously treated with the other drug they were not randomised to, patients are accounted for in the study arm according to actual treatment received. Patients who received treatment from more than one treatment arm are accounted for based upon their initial treatment started. As of the data cut-off date, the SAS included 260 patients in the olaparib arm and 130 patients in the placebo arm.¹

Treatment Exposure

The median total treatment duration in the olaparib arm was 106.9 weeks (approximately 24.6 months), ranging from 0 to 226 weeks, compared to 60.3 weeks (~13.9 months), ranging from 1 to 198 weeks. The proportion of patients

with dose interruptions in the olaparib arm was higher, with 61.2% (n=159) having any dose interruption and 26.9% (n=70) having ≥ 3 dose interruptions. In contrast, 30.8% (n=40) of patients in the placebo group had dose interruptions, with 5.4% (n=7) having ≥ 3 dose interruptions. The primary reason for a dose interruption was due to AEs in both treatment groups (49.2% and 16.2% in the olaparib and placebo arms, respectively).²

The proportion of patients with a dose reduction was higher in the olaparib arm, with 36.2% (n=94) having any dose reduction, and 19.2% (n=50) had 2 or more dose reductions. In contrast, 8.5% (n=11) of patients in the placebo group had a dose reduction and 3% (n=4) had 2 or more dose reductions.² The protocol only allowed for 2 dose reductions (from 300 mg twice a day to 250 mg twice a day to 200 mg twice a day), however, some patients had more than 2 dose reductions due to patients forgetting to take a dose which was incorrectly entered as a dose reduction in the eCRF.⁸ The primary reason for a dose reduction was due to AEs in both treatment groups (28.8% and 3.8% in the olaparib and placebo arms, respectively).²

Total daily dose of olaparib is summarised in Table 6.6. Of patients still on treatment at each time period, 80.4% received the full intended dose up to 3 months, whereas 67.9% of those received the full dose on treatment longer than 12 months.¹ Cumulatively at 24 months, 44.2% in the olaparib arm and 27.7% in the placebo arm had continued on treatment up to and including the 24 months.^{1,2} This indicated that less than half of patients continued treatment for the full 2 years with olaparib.

Adverse Events (AEs)

In the olaparib treatment arm 98.5% (n=256) of participants experienced any grade AEs, and 39.2% (n=102) of participants experienced grade 3-4 AEs compared to 92.3% (n=120) of participants in the placebo arm who experienced any grade AEs and 18.5% (n=24) who experienced grade 3-4 AEs (Table 6.11).¹

In the olaparib arm, the most common any grade AEs included nausea (n=201; 77%), fatigue or asthenia (n=165; 63%), vomiting (n=104; 40%), anemia (n=101; 39%), and diarrhea (n=89; 34%). Most AEs occurring at $\geq 10\%$ frequency in the olaparib arm were known, with the exception of constipation (n=72; 28%), dyspnoea (n=39; 15.0%), and urinary tract infections (n=31; 11.9%).⁸ The most common any grade AEs in the placebo arm included fatigue or asthenia (n=54; 42%), nausea (n=49; 38%), arthralgia (n=35; 27%), diarrhea (n=32; 25%), and headache (n=31; 24%). Anemia and neutropenia were the most common grade 3 or 4 AEs in the olaparib arm, which occurred in 22% (n=56) and 9% (n=22) of patients, respectively. In the placebo arm, neutropenia was the most common grade 3 or 4 AE, which occurred in 5% (n=6) of patients.¹ The median times and duration of first event of nausea, vomiting, fatigue/asthenia, anemia, neutropenia, and thrombocytopenia were also explored. Of note, the onset of thrombocytopenia was sooner in the olaparib arm at 2.83 months compared to 7.39 months in the placebo arm. Fatigue/asthenia lasted about a month longer in patients treated with olaparib (3.48 months) compared to placebo (2.30 months). All AEs (nausea, vomiting, fatigue/asthenia, anemia, neutropenia, and thrombocytopenia) led to a higher proportion of dose interruptions, reductions, and discontinuations in the olaparib arm compared to placebo. Anemia led to a significantly higher proportion of patients having a dose interruption in the olaparib arm (22%) compared to placebo (1%) as well as dose reduction in the olaparib arm (17%) compared to placebo (1%).⁶

Serious adverse events (SAEs)

Serious AEs (SAEs) occurred in 20.8% (n=54) of patients in the olaparib arm compared to 12.3% (n=16) in the placebo group.² Anemia was the most common SAE in the olaparib arm followed by urinary tract infection, which occurred in 17 (6.5%) and 3 (1.2%) patients, respectively, compared to no patients in the placebo arm. Breast cancer was the most common SAE in the placebo arm and occurred in 3 (2.3%) of patients compared to 1 (0.4%) of patients in the olaparib arm. Acute myeloid leukemia (AML) occurred in 3 (1%) patients in the olaparib group and no AML occurred in the placebo arm. Overall, new primary cancers occurred in 5 (1.9%) patients in the olaparib arm and 3 (2.3%) patients in the placebo arm. Pneumonitis or interstitial lung disease occurred in 5 (1.9%) patients in the olaparib arm and no patients in the placebo arm.¹

Deaths

There were no AEs with an outcome of death on study treatment of during the 30-day follow-up period. There were 4 deaths that occurred for other reasons other than those reported to be related to the disease under investigation. Two patients in the olaparib arm had AEs of AML, and deaths occurred after the 30-day follow-up period. One patient experienced septic shock, and another had an intentional overdose (suicide by means of carbon monoxide overdose). The two deaths due to AMLs were considered to be related to olaparib treatment. The patient that died from septic shock had developed a SAE of myeloproliferative neoplasm related to olaparib, which was then treated by autologous stem cell transplantation that led to the development of sepsis and resulted in fatality. This was also considered related to olaparib treatment. The fatality due to intentional overdose was not considered to be related to olaparib treatment.²

Table 6.11: Summary of adverse events in the SOLO1 trial, SAS population

Adverse Event	Olaparib (N=260)		Placebo (N=130)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	<i>number of patients (percent)</i>			
Any	256 (98)	102 (39)	120 (92)	24 (18)
Nausea	201 (77)	2 (1)	49 (38)	0
Fatigue or asthenia	165 (63)	10 (4)	54 (42)	2 (2)
Vomiting	104 (40)	1 (<1)	19 (15)	1 (1)
Anemia†	101 (39)	56 (22)	13 (10)	2 (2)
Diarrhea	89 (34)	8 (3)	32 (25)	0
Constipation	72 (28)	0	25 (19)	0
Dysgeusia	68 (26)	0	5 (4)	0
Arthralgia	66 (25)	0	35 (27)	0
Abdominal pain	64 (25)	4 (2)	25 (19)	1 (1)
Neutropenia‡	60 (23)	22 (9)	15 (12)	6 (5)
Headache	59 (23)	1 (<1)	31 (24)	3 (2)
Dizziness	51 (20)	0	20 (15)	1 (<1)
Decreased appetite	51 (20)	0	13 (10)	0
Upper abdominal pain	46 (18)	0	17 (13)	0
Dyspepsia	43 (17)	0	16 (12)	0
Cough	42 (16)	0	28 (22)	0
Back pain	40 (15)	0	16 (12)	0
Dyspnea	39 (15)	0	7 (5)	0
Thrombocytopenia§	29 (11)	2 (1)	5 (4)	2 (2)
Led to discontinuation of intervention	30 (12)	NA	3 (2)	NA
Led to dose reduction	74 (28)	NA	4 (3)	NA
Led to dose interruption	135 (52)	NA	22 (17)	NA

Source: From New England Journal of Medicine, Moore K, Colombo N, Scambia G, et al. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer, Volume No. 379, Issue 26, Page 2503. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

6.4 Ongoing Trials

No relevant ongoing studies were identified that fit the systematic review protocol.

7 SUPPLEMENTAL QUESTIONS

No relevant supplemental question was identified by the pCODR review team.

8 COMPARISON WITH OTHER LITERATURE

No relevant published literature was identified by the pCODR review team.

9 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Genitourinary Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on olaparib (Lynparza) for ovarian cancer. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the CADTH website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Economic Guidance Report was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no information redacted from this publicly available Guidance Report.

This Initial Economic Guidance Report is publicly posted at the same time that a pERC Initial Recommendation is issued. A Final Economic Guidance Report will be publicly posted when a pERC Final Recommendation is issued. The Final Economic Guidance Report will supersede this Initial Economic Guidance Report.

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

APPENDIX A: LITERATURE SEARCH STRATEGY AND DETAILED METHODOLOGY

1. Literature search via Ovid platform

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** April 2019, **Embase** 1974 to 2019 May 02, **Ovid MEDLINE(R) ALL** 1946 to May 01, 2019

Line #	Search Strategy
1	(Lynparza* or Linparza* or Lyhnpzarza* or Olaparib* or AZD-2281 or AZD2281 or KU-59436 or KU59436 or KU-0059436 or KU0059436 or WOH1JD9AR8).ti,ab,ot,kf,kw,hw,rn,nm.
2	Genital Neoplasms, Female/ or exp Ovarian Neoplasms/ or Fallopian Tube Neoplasms/ or Peritoneal Neoplasms/
3	((ovarian or ovary or ovaries or ovarial or ovarium or ((fallopian or uterine) adj2 tube*) or oviduct* or peritoneal or peritoneum or adnexa or adnexal) adj5 (Cancer* or neoplasia or neoplasm* or tumor* or tumour* or carcinoma* or malignan*)).ti,ab,kf.
4	2 or 3
5	1 and 4
6	5 use medall
7	5 use cctr
8	*Olaparib/
9	(Lynparza* or Linparza* or Lyhnpzarza* or Olaparib* or AZD-2281 or AZD2281 or KU-59436 or KU59436 or KU-0059436 or KU0059436).ti,ab,kw,dq.
10	female genital tract tumor/ or female genital tract cancer/ or exp ovary tumor/ or exp peritoneum cancer/ or uterine tube tumor/ or uterine tube carcinoma/
11	((ovarian or ovary or ovaries or ovarial or ovarium or ((fallopian or uterine) adj2 tube*) or oviduct* or peritoneal or peritoneum or adnexa or adnexal) adj5 (Cancer* or neoplasia or neoplasm* or tumor* or tumour* or carcinoma* or malignan*)).ti,ab,kw.
12	8 or 9
13	10 or 11
14	12 and 13
15	14 use oemezd

16 15 and conference abstract.pt.

17 limit 16 to yr="2014 -Current"

18 15 not conference abstract.pt.

19 (Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or
Equivalence Trial or Clinical Trial, Phase III).pt.

20 Randomized Controlled Trial/
exp Randomized Controlled Trials as Topic/
"Randomized Controlled Trial (topic)"/

23 Controlled Clinical Trial/
exp Controlled Clinical Trials as Topic/
"Controlled Clinical Trial (topic)"/

26 Randomization/
Random Allocation/
Double-Blind Method/
Double Blind Procedure/
Double-Blind Studies/
Single-Blind Method/
Single Blind Procedure/
Single-Blind Studies/
Placebos/
Placebo/
Control Groups/
Control Group/
(random* or sham or placebo*).ti,ab,hw,kf,kw.
((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.
((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.
(control* adj3 (study or studies or trial* or group*)).ti,ab,kf,kw.
(Nonrandom* or non random* or non-random* or quasi-random* or
quasirandom*).ti,ab,hw,kf,kw.

43 allocated.ti,ab,hw.

44 ((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw.

- 45 ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*).ti,ab,hw,kf,kw.
- 46 (pragmatic study or pragmatic studies).ti,ab,hw,kf,kw.
- 47 ((pragmatic or practical) adj3 trial*).ti,ab,hw,kf,kw.
- 48 ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*).ti,ab,hw,kf,kw.
- 49 (phase adj3 (III or "3") adj3 (study or studies or trial*).ti,hw,kf,kw.
- 50 or/19-49
- 51 6 or 17 or 18
- 52 50 and 51
- 53 7 or 52
- 54 limit 53 to english language
- 55 remove duplicates from 54

2. Literature search via PubMed

A limited PubMed search was performed to retrieve citations not found in the MEDLINE search.

Line #	Search Strategy
<u>#6</u>	Search #4 AND #5 Filters: Publication date from 2014/01/01 to 2019/12/31; English
<u>#5</u>	Search Publisher[sb] Filters: Publication date from 2014/01/01 to 2019/12/31; English
<u>#4</u>	Search #1 AND (#2 OR #3) Filters: Publication date from 2014/01/01 to 2019/12/31; English
<u>#3</u>	Search (Ovarian[tiab] OR ovary[tiab] OR ovaries[tiab] OR ((fallopian[tiab] OR uterine[tiab]) AND tube[tiab]) OR oviduct*[tiab] OR peritoneal[tiab] OR peritoneum[tiab] OR adnexa[tiab] OR adnexal[tiab]) AND (Cancer*[tiab] OR neoplasia[tiab] OR neoplasm*[tiab] OR tumor[tiab] OR tumors[tiab] OR tumour[tiab] OR tumours[tiab] OR carcinoma*[tiab] OR malignan*[tiab]) Filters: Publication date from 2014/01/01 to 2019/12/31; English
<u>#2</u>	Search Genital Neoplasms, Female[mh:noexp] OR Ovarian Neoplasms[mh] OR Fallopian Tube Neoplasms[mh] OR Peritoneal Neoplasms[mh] Filters: Publication date from 2014/01/01 to 2019/12/31; English
<u>#1</u>	Search Lynparza*[tiab] OR Linparza*[tiab] OR Lyhnpzarza*[tiab] OR Olaparib*[tiab] OR AZD-2281[tiab] OR AZD2281[tiab] OR KU-59436[tiab] OR KU59436[tiab] OR KU-

Line #	Search Strategy
	0059436[tiab] OR KU0059436[tiab] OR WOH1JD9AR8[tiab] Filters: Publication date from 2014/01/01 to 2019/12/31; English

3. Cochrane Central Register of Controlled Trials (CENTRAL)
(searched via Ovid)

4. Grey literature search via:

Clinical trial registries:

US National Library of Medicine. ClinicalTrials.gov
<https://clinicaltrials.gov/>

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
<http://www.canadiancancertrials.ca/>

Search: olaparib (lynparza), ovarian cancer

Select international agencies including:

US Food and Drug Administration (FDA)
<https://www.fda.gov/>

European Medicines Agency (EMA)
<https://www.ema.europa.eu/>

Search: olaparib (lynparza), ovarian cancer

Conference abstracts:

American Society of Clinical Oncology (ASCO)
<https://www.asco.org/>

European Society for Medical Oncology (ESMO)
<https://www.esmo.org/>

Search: olaparib (lynparza), ovarian cancer – last five years

APPENDIX B: Detailed Methodology of Literature Review

Literature Search Methods

The literature search for clinical studies was performed by an information specialist from the pCODR Methods Team using the abovementioned search strategy, which was peer-reviewed according to the PRESS (Peer Review of Electronic Search Strategies) checklist (<https://www.cadth.ca/resources/finding-evidence/press>).⁴⁸

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, the Cochrane Central Register of Controlled Trials (CENTRAL) via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine’s MeSH (Medical Subject Headings), and keywords. The main search concepts were lynparza (olaparib) and ovarian cancer.

Search filters were applied to limit retrieval to randomized controlled trials or controlled clinical trials. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents but not limited by publication year.

The search is considered up to date as of August 28, 2019.

Grey literature (literature that is not commercially published) was identified by searching websites from relevant sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist (<https://www.cadth.ca/grey-matters>).⁴⁹

Included in this search were the websites of regulatory agencies (US Food and Drug Administration and European Medicines Agency), clinical trial registries (US National Institutes of Health’s clinicaltrials.gov and Canadian Partnership Against Cancer Corporation’s Canadian Cancer Trials), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) were searched manually for conference years not available in Embase. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the CADTH Clinical Guidance Panel. As well, the manufacturer of the drug was contacted for additional information, as required by the pCODR Review Team.

Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. Two members of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

Data Analysis

No additional data analyses were conducted as part of the pCODR review.

Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups, by the Provincial Advisory Group (PAG), and by Registered Clinicians.

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